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COMPLICATIONS OF INFANTILE ECZEMA CAUSED BY THE VIRUS OF HERPES SIMPLEX

(*a*) DESCRIPTION OF THE CLINICAL CHARACTERISTICS OF AN UNUSUAL ERUPTION AND (*b*) IDENTIFICATION OF AN ASSOCIATED FILTRABLE VIRUS

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The disturbed integument of infants and children ill with eczema is infected frequently by bacterial "opportunists" [1] and less often by filtrable viruses. Of the latter, the virus of vaccinia, chiefly as a cause of eczema vaccinatum, has been recognized more frequently than any other.[2] There remains a group of cutaneous eruptions complicating infantile eczema that resemble the pocklike lesions of vaccinia, variola and varicella, although the clinical course is different. Among these is Kaposi's "eczema herpetiforme," the cause of which is obscure. In the present report evidence is presented to implicate the virus of herpes simplex in the causation of an eruption appearing in infants with eczema. The clinical features of the disease these infants had were like those Kaposi described.[3]

In the past year 3 infants were observed in the New Haven Hospital, each presenting in the course of his illness a similar and, in the experience of the staff, unusual type of cutaneous eruption. One of the infants soon died; the others, although seriously ill, recovered. The present report describes (*a*) the clinical characteristics of the disease in these infants, (*b*) the detection of a filtrable virus in the brain of a child who had died of the disease and in exudate from the cutaneous lesions of all of the patients and (*c*) the identification of each of the three strains as the virus of herpes simplex.

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1. Boisvert, P. L.; Darrow, D. C.; Powers, G. F., and Trask, J. D.: Streptococcosis in Children: A Nosographic and Statistical Study, Am. J. Dis. Child. **64**:516 (Sept.) 1942.

2. Ross, R. A.: Generalized Vaccinia, in Virus and Rickettsial Diseases: A Symposium Held at the Harvard School of Public Health, 1939, Cambridge, Mass., Harvard University Press, 1940, pp. 217-225.

3. Kaposi, M. J.: Pathologie und Therapie der Hautkrankheiten, Berlin, Urban & Schwarzenberg, 1887, p. 483.

CLINICAL REPORTS

In the first patient (B. A. C.) the condition was fatal. An infectious agent in the exudate from vesicles in the skin of this patient was capable of provoking encephalitis and keratoconjunctivitis in the rabbit subsequent to inoculation of the material into the scarified cornea. Also, tissue from the brain of B. A. C. caused fatal encephalitis in rabbits.

CASE 1.—*History.*—B. A. C., a girl aged 5 months, was admitted to the New Haven Hospital Feb. 20, 1942, with a history of eczema of four months' duration. She had been breast fed for the first five weeks of life. When she was 1 month of age a rough, patchy papular rash appeared on her forehead and spread quickly to her cheeks. In the following two months the "eczema" spread to the chest, arms and legs. Although the composition of the infant's food was twice changed and local treatment was applied, the character of the rash remained unchanged. On February 19 the baby became irritable and refused to eat. Her mother thought that she had fever; a physician found that the baby had a temperature of 103 F., an injected throat and redness and lacrimation of the eyes. The patient was worse the following day, when her temperature was 104 F. The mother was of the opinion that a new rash had appeared on the skin of the face, scalp and abdomen. Then the baby was brought to the hospital.

The history of her birth was not unusual. There was a family history of eczema. The baby had not been vaccinated or exposed to any person recently vaccinated, and no one had been ill at home.

Physical Examination.—The baby's temperature was 105.2 F. (rectal) on her admission to the hospital. She appeared well developed, well nourished and not acutely ill. The skin of the scalp, face, thorax, hands and legs was the seat of discrete, almost confluent papules, which were umbilicated and surrounded by a narrow zone of erythema. The average diameter of the papules was 3 mm. A few of the cutaneous lesions were pustules. The buccal mucous membrane was reddened, and the mesopharynx was injected. A papulopustular lesion was present on the buccal mucosa on the left side, and similar but smaller lesions were seen on the right. The cardiac, pulmonary and neurologic signs were not abnormal.

Clinical Course.—Figure 1 and table 1 illustrate the clinical course of patient B. A. C. during her residence in the hospital. During the first few days of illness many of the papules became vesicles and then pustules. The time required for vesicles to undergo transition to

the pustular stage was short, usually less than twenty-four hours. Many of the pustules became hemorrhagic and contained a brown-red exudate. On the third day in the hospital the patient had numerous bullae, partially filled with a turbid yellow fluid, on the face and forehead. When these bullae disintegrated, fluid was released, which when dry formed a gray-yellow crust. Removal of the crust exposed a "punched-out" crater whose base was red and granular. Gradually, during the next two days the eruption spread by confluence to involve most of the face, trunk and shoulder girdle. Disseminated lesions were present on the arms and legs. More extensively involved areas of the integument were separated from those less extensively involved by narrow margins of apparently uninvolved skin. At the time of the child's death, that which previously had been a confluent (or disseminated) pustular, crusted exanthem had broken down, leaving red, crusted subcutaneous tissue exposed to view. Figure 2 shows the distribution of the cutaneous lesions following the death of the patient.

The patient passed a tarry stool on the second day in the hospital. No evidence of hypoprothrombinemia was demonstrated.[4] Flexure twitchings of the right arm and leg and clonic contractures of the left arm occurred on the fourth day in the hospital. The infant had mild convulsions and regurgitated frequently. As suggested by the lowered level of calcium in the serum, these symptoms may have been due to tetany. On February 26 dulness and rales were present over the bases of both lungs. The subcutaneous tissues of the abdomen and lower extremities became scleremic. The infant died on the following day, her seventh in the hospital.

Laboratory Data.—(*a*) Exudate from vesicles on the face and shoulder of patient B. A. C. obtained on February 22 and inoculated on the scarified cornea of rabbit's eye provoked keratoconjunctivitis and encephalitis in the animal. The methods used in the identification of this agent are described, and its relation to the disease in question is discussed later in this paper.

(*b*) Cultures of material from the nose and throat, made on February 20, both contained staphylococci and that from the throat contained Micrococcus catarrhalis in addition. Exudate from the child's nose and throat inoculated into the peritoneal cavity of a mouse subsequently killed it, and a pure culture of Haemophilus influenzae type B was grown from the animal's peritoneal fluid. The cultures of material from the cutaneous lesions demonstrated staphylococci only. Cultures of blood were made on February 20, 21 and 22. All except one, which was contaminated with Staphylococcus albus, were bacteriologically sterile.

(*c*) On February 23 there were 8 lymphocytes per cubic millimeter of spinal fluid. The chemistry of the spinal fluid was normal. Leukocyte counts ranged from 9,100 to 13,199 cells per cubic millimeter of blood; the differential count was not remarkable. The blood contained 28 mg. of nonprotein nitrogen, 8.5 mg. of calcium and 4.1 mg. of phosphorus per hundred cubic centimeters on February 23. Further tests, on February 26, showed total protein 4.6 per cent, albumin 3.2 per cent, potassium 6.8 millimols per liter, chlorides 138 milliequivalents per liter and sodium 163 milliequivalents per liter. Post mortem neither the blood nor the spinal fluid contained bacteria demonstrable by smear or culture.

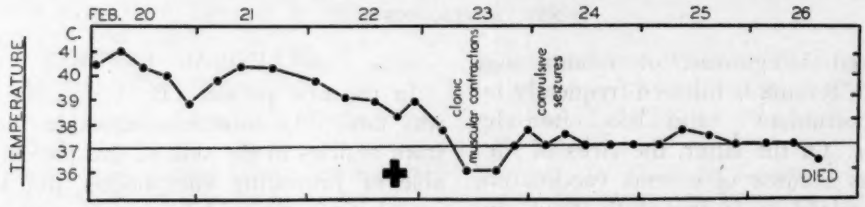

Fig. 1.—Chart of the clinical course of patient B. A. C. The position of the cross indicates the date on which the virus was isolated from cutaneous exudate.

TABLE 1.—*Clinical Laboratory Data for Patient B. A. C.*

							Post Mortem		
	Feb. 20	21	22	23	24	25	26 A. M.	26 P. M.	27
Leukocytes: number per cu. mm. of blood	13,100	9,100	.....	10,550	.....	9,700			
Bacteria present:									
Nose	Staphylococci								
Throat	Staphylococci, M. catarrhalis								
Skin	Staphylococci								
Blood: In broth	.....	Staph. albus	None	None	.....	.....	....	....	None
Blood: Pour plate	.....	None	None	None	.....	.....	....	....	None
Cerebrospinal fluid	.....	.....	.....	.....	None	.....	....	....	None
Virus isolated	.....	From skin	.....	.....	.....	.....	....	....	From brain
Blood chemistry:									
Nonprotein nitrogen	.....	.....	.....	28.0 mg. /100 cc.					
Calcium	.....	.....	.....	8.5 mg. /100 cc.					
Phosphorus	.....	.....	.....	4.1 mg. /100 cc.					
Sulfonamide compounds, Gm	0.5	1.0	1.0	1.0	1.0	1.0	1.0		

4. Lawson, R. B.: Treatment of Hypoprothrombinemia (Hemorrhagic Disease) of the Newborn Infant, J. Pediat. **18**:224 (Feb.) 1941.

Necropsy (Reported by Dr. Black-Sheppard).—The distribution and character of the dermal lesions have been noted. The viscera showed no abnormal gross or microscopic changes except focal pulmonary atelectasis. The cerebral leptomeninges were edematous but thin and translucent. A minimal amount of blood pigment was present in the subarachnoid space, overlying the right parietal region. The brain was symmetrically developed, and no abnormalities were evident on external examination. In frontal sections, the cortex and medulla were well demarcated. The brain was somewhat edematous; however, there were no gross abnormalities present. There was a small, circumscribed area of vascular congestion in the cortex of the tip of the left occipital lobe.

Sections through the skin of the chest and leg showed crateriform lesions characterized by necrosis (and disappearance) of the stratified squamous epithelium, leaving the papillae intact in outline. The fibrocytes of the papillae were pyknotic and showed fragmentation and loss of cytologic detail. A scant infiltration by round cells was seen in the superficial layers of the corium. The deeper accessory structures, hair follicles, sebaceous glands and subcutaneous tissues, were not involved.

Sections taken from the hippocampus, the periventricular gray matter, the frontal, parietal and occipital

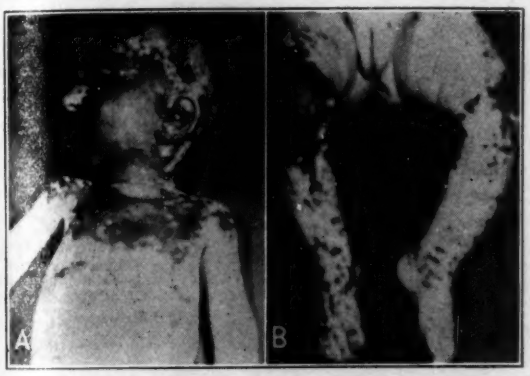

Fig. 2.—Photographs of patient B. A. C., taken post mortem, showing the distribution of the cutaneous lesions.

lobes, the cerebellum and the medulla were examined by Dr. H. M. Zimmerman. There was no inflammation in either the brain or the leptomeninges, and there was no destructive lesion in the sections examined. The only change was a swelling of the individual ganglion cells accompanied with a loss of tigroid substance without a loss of the cell membrane.

Nevertheless, brain tissue obtained from the parietal lobe just posterior to the fissure of Rolando when inoculated into rabbits *produced encephalitis in them.*

The second patient (F. H. E.) recovered from this illness. An infective agent recovered from the cutaneous lesions of this patient was capable of inducing keratoconjunctivitis in rabbits.

Case 2.—F. H. E., a boy 20 months old, was admitted to the New Haven Hospital on April 11, 1942 because of severe eczema of six months' duration. When he was 14 months of age a red, dry papular rash had appeared on the skin in the popliteal and antecubital spaces. The rash spread up the legs, and later blisters appeared around the umbilicus. He had a temperature of 105 F. After treatment with one of the sulfonamide compounds he had a diffuse rash over the body and passed loose, green stools. Subsequently, he is said to have had mild bouts of fever. When the patient was 16 months of age his skin was described as moist, cracked, oozing and peeling. He was admitted to a hospital because of the severity of the condition of his skin and the onset of fever with pharyngitis. Cultures of the skin were reported to his parents as "negative for impetigo." The infant had a generalized edema at this time. He improved slowly and was discharged from the hospital after two months. When he was 19 months old, new cutaneous lesions that resembled impetigo appeared on areas of weeping eczema. The impetiginous lesions spread from the legs to involve the buttocks and arms and the back of the neck. The lesions improved after treatment with merthiolate. The eczema subsided to a chronic state until March 1942, when the involved areas again oozed, crusted and peeled. Persistent, generalized edema appeared. Three weeks later, April 11, 1942, he was referred to the New Haven Hospital for treatment.

The history of the child's birth was normal. No history of allergy in the family was elicited. The baby had not been vaccinated or exposed to any one recently vaccinated.

Physical Examination.—The baby had a temperature of 98.2 F. on admission to the hospital. There was generalized edema. The face was puffy, and the eyes were almost swollen shut. The skin of the whole body was fiery red, especially over the thorax and abdomen. These areas were sites of desquamation of large scales of epidermis. The skin over the scrotum, knees and legs was taut and appeared leathery. There was generalized lymphadenopathy. A coarse tremor of the right hand was noted. The mucous membrane of the mouth and mesopharynx was not unusual. The cardiac, pulmonic and neurologic signs showed no abnormality.

Laboratory Data.—(*a*) Fluid obtained on the third day of the rash (April 21, 1942) from vesicles on the face and trunk of F. H. E. was instilled on the scarified cornea of a rabbit's eye, and three days later a keratoconjunctivitis developed. Hemolytic streptococci were obtained from a culture of the vesicular fluid employed in the inoculation of the rabbit.

(*b*) No pathogenic bacteria were observed in cultures of the exudates from the nose and throat (April 11, 1942). Swab cultures from the cutaneous lesions yielded hemolytic streptococci, group A, type 14.[5] Cultures made on mediums suitable for the growth of fungi failed to reveal any. A culture of the blood (April 11, 1942) was bacteriologically sterile.

(*c*) The leukocyte count dropped from 48,700 cells per cubic millimeter of blood on the patient's admission to 11,400 on April 20, when the cutaneous eruption was at its height. After the child recovered from his "new" eruption the leukocyte count rose again and remained high, with further elevations during acute febrile episodes (fig. 3 and table 2). The total serum proteins amounted to 3.4 per cent, and the serum cholesterol content was 165 mg. per hundred cubic centimeters.

Other laboratory data were noncontributory.

Clinical Course.—Figure 3 and table 2 illustrate the clinical course of patient F. H. E., which was satisfactory during the first five days that he was in the hospital. On the sixth day a new exanthem appeared, consisting of red papules, 2 to 3 mm. in diameter, distributed diffusely over the skin of the scalp and trunk. Within twenty-four to thirty-six hours similar papules appeared on the face and extremities. The hands and feet were bright red and swollen; their appearance was similar to that seen in acrodynia. A few scattered

5. Dr. P. L. Boisvert supplied this information.

vesicles on the fingers and toes contained a turbid exudate. The tongue was unusually smooth. A few reddened "spots" similar to those on the skin appeared on the soft palate and buccal mucosa.

The baby, although seriously ill at this time, became increasingly so during the next ten days. The character of the eruption changed from papules to vesicles and

Although the chief concern here is with the three weeks of the child's illness just described, his ten months of illness in the hospital, illustrated in part in figure 3 and in table 2, calls attention to the difficulties met with in freeing his scarred integument of bacterial "opportunists." Two attempts to detect in the skin of F. H. E. an infectious agent related to the one found

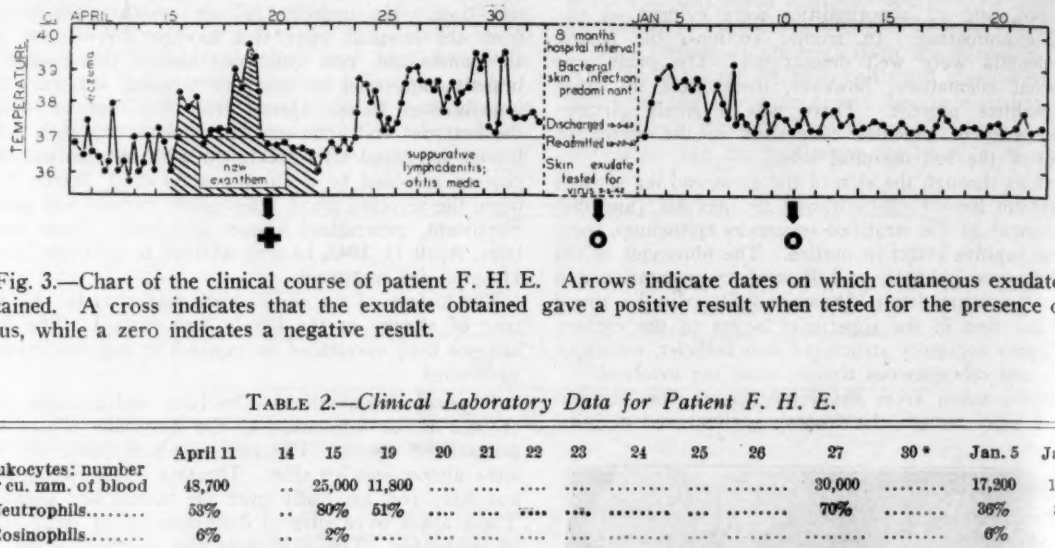

Fig. 3.—Chart of the clinical course of patient F. H. E. Arrows indicate dates on which cutaneous exudate was obtained. A cross indicates that the exudate obtained gave a positive result when tested for the presence of the virus, while a zero indicates a negative result.

TABLE 2.—*Clinical Laboratory Data for Patient F. H. E.*

	April 11	14	15	19	20	21	22	23	24	25	26	27	30 *	Jan. 5	Jan. 20
Leukocytes: number per cu. mm. of blood	48,700	..	25,000	11,800	....	....	....	....	.....	...	.....	30,000	.....	17,200	18,900
Neutrophils.....	53%	..	80%	51%	....	....	....	....	.....	...	.....	70%	.....	36%	34%
Eosinophils.....	6%	..	2%	....	....	....	....	....	.....	...	.....	.....	.....	6%	
Lymphocytes.....	35%	..	20%	44%	....	....	....	....	.....	...	.....	30%	.....	53%	64%
Monocytes.....	3%	..	....	2%	....	....	....	....	.....	...	.....	.....	.....	3%	2%
Bacteria present:															
Nose.....	M. catarrhalis Staphylococci Diphtheroids		....	....	....	....	....	....	.....	...	Staph. albus	.....	.....	Staph. aureus	Staph. aureus
Throat.....	"Green streptococci" H. influenzae M. catarrhalis	..	....	....	....	....	....	....	.....	...	Str. haemolyticus D. pneumoniae XVIII Staphylococci "Green streptococci"	.....	.....	"Green streptococci" Staph. albus	"Green streptococci" M. catarrhalis
Skin.....	Str. haemolyticus Staphylococci	..	....	....	....	....	....	....	Str. haemolyticus Staphylococci	....	.....	.....	Staph. aureus Mannitol + coagulase + Str. haemolyticus	Staph. albus Str. haemolyticus	
Blood.....	None														
Ear.....	B. coli														
Occipital abscess...	.....	..	....	....	....	....	....	....	.....	...	.....	Staphylococci Diphtheroids, Str. haemolyticus			
Fungi present (by microscopy and culture; cutaneous exudate)	.....	..	None												
Sulfonamide drugs, Gm.....	.....	..	....	1.25	1.25	0.75	2.25	2.25	2.25						
Transfusions, Cc.....	.....	200	100	....	200	300	....	....	200	200	200				

* Interval of 8 months following April 30. Patient hospitalized. Discharged 10/5/42. Readmitted 10/22/42.

later to pustules. Almost all of the integument was involved. New crops of papules appeared and ran a transitional course requiring twenty-four to forty-eight hours to reach the pustular stage. A few, but not many, of the pustules became confluent. The pustules measured on the average 4 to 5 mm. in diameter. They regressed in four to five days, leaving the surface of the skin defaced by clusters of punched-out, reddened ulcers which healed rapidly. The early lesions and the later punched-out residua (temporary) occurring in the skin of F. H. E. are illustrated in figure 4.

originally in the exudate used for the inoculation of a rabbit were not successful; they were made in his sixth and tenth months in the hospital.

The condition of the patient's skin vacillated from better to worse. A purulent otitis media occurred; the aural exudate on culture contained hemolytic streptococci. The lymph nodes in the occipital triangle and in the left axilla suppurated; those in the occipital area formed open abscesses. Hemolytic streptococci were cultured from the exudate. Aspiration of the axillary lymph nodes provided a small amount (0.5 cc.) of turbid

yellow fluid that yielded staphylococci on culture. F. H. E.'s leukocyte count fluctuated between 15,000 and 46,000 cells per cubic millimeter of blood. Cultures of material from the surface of the nasopharynx irregularly contained hemolytic streptococci. Occasionally, classifiable pneumococci were found. The suppurating lymphadenitis and dermatitis were treated with sulfadiazine by mouth and with soaks in sulfanilamide solution, but not constantly. The patient improved slowly and was discharged from the hospital on Oct. 4, 1942. Three weeks later he was admitted again because his eczema had become worse. Hemolytic streptococci were obtained in cultures of exudates from the skin and the nasopharynx. Treatment on this admission consisted of administration of sulfadiazine by mouth, application of sulfathiazole ointment and, later, soaks of the affected skin in penicillin solution. Although hemolytic streptococci were infrequently isolated after this treatment was begun, other bacteria, chiefly those of the coliform and enterococcic groups, were isolated frequently. The child slowly improved. He was discharged from the hospital on Feb. 4, 1943.

contiguous areas of skin, a physician advised that the baby be sent to a hospital (May 25, 1943).

According to the history, the child's birth was normal. No one had been ill at home. The infant had not been vaccinated or exposed to any one recently vaccinated.

Physical Examination.—The baby's temperature was 105 F. when she was admitted to the hospital. Her pulse was rapid. She appeared acutely and chronically ill. A dry, scaling eczematous rash was present over almost all of the integument; in some areas the skin was somewhat thickened and indurated. An exceptional eruption consisting of discrete vesicles and umbilicated pustules was present over the left side of the scalp and face and, to a less extent, on the left shoulder and arm. The vesicles measured, on an average, 2 to 3 mm.; the pustules were larger (4 to 5 mm.) and somewhat yellow. Many of the lesions were surrounded by a narrow zone of erythema. There was generalized lymphadenopathy involving the superficial anterior cervical, posterior cervical, posterior auricular, posterior occipital, axillary and inguinal lymph nodes. The left eyelid and palpebral conjunctiva were inflamed. The

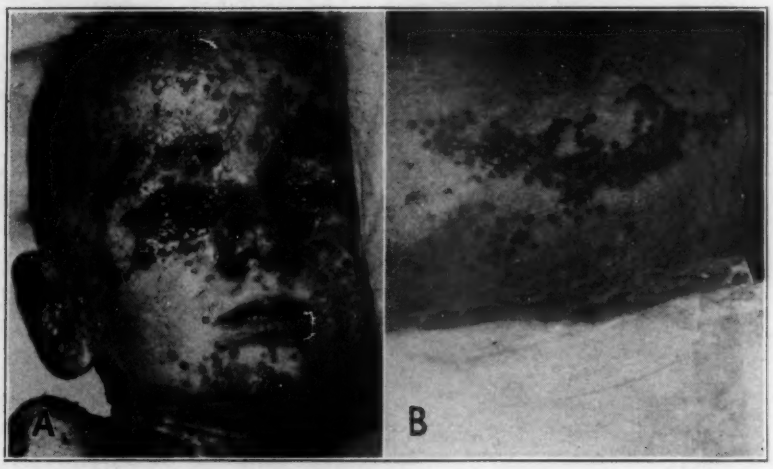

Fig. 4.—Photographs of patient F. H. E. (*a*) on the third day of illness, showing the early character of the lesions, and (*b*) on the eleventh day of illness, showing the punched-out residua.

The third child (S. F.), although severely ill, recovered from her illness also. An infectious agent capable of provoking keratoconjunctivitis and encephalitis in rabbits was recovered from the cutaneous lesions of this patient.

CASE 3.—*History.*—S. F., a girl 8 months of age, was admitted to the New Haven Hospital on May 25, 1943 because of infected eczema. The baby had been well until she was 2 months of age, when a "rash" appeared on her face and forehead and thereafter soon spread over the surface of the body. Although the infant was treated by the institution of various diets (including, among others, goat's milk) and with numerous ointments applied locally, the character of the eczematous lesions changed little in the next six months. On May 23 the eczema seemed worse; there was exudation of serous fluid which dried and crusted. Some of the lesions oozed a purulent exudate. The baby was anorexic and irritable; she scratched continuously and seemed to the mother to be extremely warm. The following day the infant was seriously ill, and a new rash appeared on the scalp and face. Inasmuch as there was no improvement and the rash had spread to involve

throat was somewhat more reddened than is usual. No enanthem was noted. The spleen was not palpable. The cardiac, pulmonic and neurologic data showed no abnormality.

Clinical Course.—Figure 5 and table 3 illustrate the clinical course of patient S. F. for her first two weeks in the hospital. During the three days following admission of the patient to the hospital new discrete single vesicles and crops of them appeared on the skin of the chest, abdomen and upper and lower extremities. Elsewhere new vesicles appeared among pustules. In a brief period, usually less than thirty-six hours, the contents of the vessels became purulent. The pustules were umbilicated and unilocular. Some of them, particularly those on the face and scalp, became confluent (fourth and fifth days in the hospital) and later crusted. Only a few new lesions appeared after the fifth day in the hospital. Thereafter, crusting occurred. Discrete or confluent pustules were covered with a brown, bloody crust, particularly those on the face and scalp. If the crusts were removed the underlying corium bled freely. Only a few disintegrating pustules were evident among multiple crusted lesions at the end of the first week. Toward the end of the second week the crusts dropped away, exposing at the site of each a faintly red, granular

epithelial surface. These areas healed rapidly without evidence of scarring.

The baby was critically ill during the first week; her temperature fluctuated between 102 and 105.8 F. At the end of the first week the fever subsided, but it reappeared a few days later and persisted until the end of the second week, when the temperature returned to normal. The infant had an unexplained diarrhea for two days during the second week in the hospital. On the twenty-third day of the illness new vesicles and pustules again appeared on the skin of the trunk. These healed in a few days without crusting, and thereafter convalescence, though slow, was continuous.

Laboratory Data.—(*a*) Vesicular fluid obtained from lesions on the face and scalp of S. F. during the third and fourth days in the hospital was inoculated on the scarified cornea of each of three rabbits. In all keratoconjunctivitis developed. The remaining vesicular exudate was cleared of bacteria by passing it through a Berkefeld "N" filter, and the filtrate was inoculated intracerebrally into a rabbit. The animal manifested signs and symptoms of encephalitis seven days later.

(*b*) No pathogenic bacteria were observed in cultures of exudates from the nose and throat (May 25, 1943). Hemolytic streptococci, group C,[5] were obtained in cultures of exudate from the nasopharynx. Swab cultures of material from the cutaneous lesions also yielded hemolytic streptococci of group C. Two cultures of blood in fresh beef heart infusion broth, made on May 25 and May 30, provided diphtheroids and Staph. albus respectively. Pour plates were sterile on both occasions.

(*c*) The leukocyte count dropped from 16,250 cells per cubic millimeter of blood on the patient's admission to 9,500 on May 28. The count ranged from 8,900 to 10,550 cells during the height of the eruption.

Other laboratory data were noncontributory.

In summary, an unusual cutaneous eruption occurring in 3 infants was characterized by an eruption which passed through the stages of papules, vesicles, pustules and crust. The lesions appeared in crops, ran a transitional course lasting seven to ten days and in 2 of the infants spread by confluence to attack en masse large areas of integument. During the first week of the disease new vesicles appeared scattered among pustules; these, too, quickly became purulent (in twenty-four to thirty-six hours). The mucous membranes of the mouth were the seat of small, reddened ecchymotic lesions, measuring roughly 1 to 2 mm. in diameter (patients B. A. C. and F. H. E.). Despite much fever, there was a relative leukopenia, most evident at the peak of the eruption. One of the infants (B. A. C.) died with symptoms suggestive of encephalitis. The presence of this disease was not substantiated by antemortem examination of the spinal fluid or by postmortem microscopic study of the cerebral tissues.

Inasmuch as the disease manifested by these infants resembled other "pox" diseases, a member of the group of filtrable viruses was considered a likely etiologic agent. The early vesicles resembled those occurring in herpes simplex infections of the skin and mucous membranes. Consequently, the detection of an infectious agent in the vesicular fluid that was capable of caus-

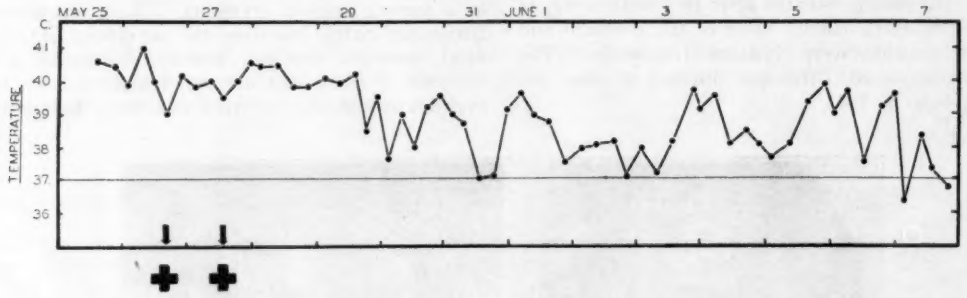

Fig. 5.—Chart of the clinical course of patient S. F. The position of the arrows indicate dates on which cutaneous exudate was obtained and the crosses times at which the virus was isolated from these exudates.

TABLE 3.—*Clinical Laboratory Data for Patient S. F.*

	May 25	26	27	28	29	30	31	June 1	2	3	4	5	6	7
Leukocytes: number per cu. mm. blood.....	16,250	..	..	9,500	..	..	10,550	...	8,900	...	...	...	...	5,250
Bacteria present:														
Nose.....	Diphtheroids Staph. albus													
Throat.....	M. catarrhalis Str. haemolyticus, group C Staph. aureus													
Skin.....	Str. haemolyticus, group C Staph. aureus													
Blood { Broth.....	Diphtheroids	..	..	.....	..	Staph. albus								
Blood { Pour plate	None	..	..	.....	..	None								
Sulfonamide compounds, Gm.....	1.25	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	1.5	1.5	1.5

ing a herpes-like disease in rabbits was not surprising. The detection of an agent in the brain tissue from B. A. C. which was infectious for rodents was unexpected. It seemed pertinent, therefore, to identify the agents isolated and to determine their relationship to the disease in question.

ISOLATION AND IDENTIFICATION OF THE INFECTIOUS AGENTS

In the preceding clinical report it was stated that an infectious agent capable of causing keratoconjunctivitis and encephalitis was detected in the vesicular exudate from the skin of each of 3 patients and in the brain of 1 of them. These 4 strains represent the agents suspected of causing the cutaneous eruptions in the infants. In this section of the report the methods and results in respect to the isolation and identification of the infectious agents are described.

The four strains which were isolated from the 3 infants are designated hereafter as B. A. C.'s, F. H. E.'s and S. F.'s cutaneous strains, and B.A.C.'s cerebral strain. The cutaneous and cerebral strains from patient B. A. C. were considered as two distinct viruses, at least until it could be shown that they were related. S. F.'s cutaneous strain has not been studied in quite as detailed a manner as have the others, because this patient was seen recently; nevertheless, enough information concerning it is available to indicate that it is related to them.

Each strain was studied with two purposes in mind: (*a*) to ascertain the nature of the infectious agent, that is, to establish its identity, and (*b*) to show if possible that each strain was of human origin and related to the disease in question. An effort was made in the first of these studies to elucidate some of the properties of the virus in respect to infection in animals, including the range of animals susceptible to infection with it, the ability of the strain in question to cause inflammation in specific tissues, particularly in rabbits, and the pathologic changes it produced. Serologic evidence was sought then to demonstrate that each strain was related to the disease in the 3 infants. To this end neutralization tests with human serum were done. Finally, to demonstrate the relationship of each strain to the virus of herpes simplex, rabbits actively immunized with the strain to be tested were challenged with the HF strain[6] of herpes simplex virus to determine their resistance to it.

Fig. 6.—Photographs of patient S. F. (*A*) on the fourth day of illness and (*B*) on the tenth day of illness, showing the distribution and the character of the cutaneous lesions.

IDENTIFICATION

MATERIAL AND METHODS.—*Clinical Material.*—(*a*) Turbid fluid aspirated from the vesicular fluid of each of the 3 patients constituted the primary inoculums. Spinal fluid and cerebral tissue from patient B. A. C.

6. The HF strain of the virus of herpes simplex was made available for use in these experiments through the courtesy of Dr. T. M. Rivers, Hospital of the Rockefeller Institute for Medical Research, and Dr. P. K. Olitsky of the Rockefeller Institute for Medical Research, New York.

may be considered primary inoculums also. The cerebral tissue was obtained from the parietal lobe just posterior to the fissure of Rolando.

(*b*) Potentially infective material, exudate from 20 children with various cutaneous infections, such as infected eczema, impetigo contagiosum, dermatitis exfoliativa neonatorum, herpes labialis, herpetic stomatitis and herpes zoster, was employed for control purposes.

(*c*) Serum was not available from the first patient (B. A. C.), and an initial bleeding was not obtained from the second patient (F. H. E.). Serum was first obtained from F. H. E. six weeks after the onset of his illness, and thereafter at bimonthly intervals until he was discharged from the hospital. Serum was obtained from S. F. on her eighth day in the hospital and at fifteen day intervals thereafter. Serum from 20 children who did not have infected eczema was obtained for control purposes.

All materials were immediately stored in a dry ice chest (— 76 C.), unless used for inoculations.

Animals.—Rabbits, Swiss mice, hamsters, guinea pigs, albino rats, monkeys, ferrets and a dog were tested for susceptibility to the infectious agent and were used for passage of the infective organism and for tests of its presence.

All animals were observed at least twice daily for from three to five weeks. Temperatures were taken daily for the larger rodents and the monkeys.

Inoculums.—Brain tissue and, less frequently, testicular tissue were obtained from animals that died or that were killed while they were acutely ill. Sterile precautions were used during all procedures. One half of a rabbit's brain or testis or the whole brain of a smaller rodent was triturated with sterile sand or alundum [7] and diluted to make a 10 per cent aqueous suspension. The supernatant portion of this after centrifugation (2,000 revolutions per minute for ten minutes) constituted the inoculum. Inoculation of animals [8] was accomplished through intracerebral, intradermal, intratesticular, intraperitoneal, intranasal and corneal (scarified) portals. Monkeys received 0.5 cc., rabbits 0.25 cc. and mice 0.03 cc. (other rodents received 0.05 to 0.15 cc.) of the inoculums intracerebrally and amounts varying from 0.2 to 5 cc. by the other portals. Some of the inoculums were decimal dilutions of the 10 per cent suspension. These are defined later in the paper.

Cultures.—The presence or absence of ordinary bacteria in infected organs or emulsions was determined by means of aerobic and anaerobic cultures in fresh beef heart infusion broth or on blood agar plates. Loeffler's medium, Corper's medium and deep meat tubes were used also.

Filtration.—Berkefeld candles of "N" porosity and Pasteur-Chamberland filters of L_3 and L_5 porosities were used. Filtration was effected by negative air pressure, and the amount of pressure at work was controlled by inserting a mercury manometer between the filter and the suction system. The negative pressures in centimeters of mercury employed were as follows: "N" and L_5 candles, 20 cm.; L_3 candles, 30 cm. Serratia marcescens was employed to test the permeability of the filters to bacterial agents. If this bacterium was present in the filtrate the latter was not accepted for tests in animals.

Histologic Studies.—Cerebral, renal, adrenal, testicular and ocular tissues from affected animals were fixed in a 10 per cent concentration of solution of formaldehyde U. S. P. and in Zenker's 10 per cent acetic acid fixative. Tissues from these organs were also obtained from uninoculated animals for control purposes. Paraffin sections were stained with hematoxylin and eosin, with eosin–methylene blue and with Giemsa's stain. Impression smears from the brain, testis and cornea of affected rodents were stained with Wright's and Giemsa's stains and with carbolfuchsin and methylene blue according to the method of Macchiavello.[9]

Immunologic Studies.—The HF strain of the virus of herpes simplex was maintained by intracerebral passage in mice. Subsequently it was adapted to rabbits. It was in its fourth passage in rabbits when used in the protection tests.

(*a*) *Neutralization Tests.*—Freshly isolated viruses of the standard HF strain, F. H. E.'s cutaneous strain, B. A. C.'s cutaneous strain and B. A. C.'s cerebral strain were used to test the levels of neutralization of serums obtained from (1) patient F. H. E., (2) patient S. F., (3) 2 children recently recovered from a herpetic infection, (4) 18 children selected from the clientele of the Children's Clinic, (5) normal rabbits and (6) rabbits immunized with the use of four strains, B. A. C.'s cutaneous and cerebral strains, F. H. E.'s cutaneous strain and the HF strain of the virus of herpes simplex. Equal amounts (0.3 cc.) of undiluted serum and of serial tenfold dilutions of virus were incubated in a water bath at 37 C. for two hours. They then were chilled and inoculated immediately into mice to test each dilution of the virus-serum mixture; five (recently four) mice 4 weeks of age and of a standard strain [10] were used. The mice were observed for twenty-one days, and the day of death was recorded for those that died.

(*b*) Test for Active Immunity: Immunization of rabbits was attempted by repeated inoculation of them with potent strains of virus (at ten day intervals for a period of two to five months) by way of intradermal, intraperitoneal, intratesticular and intracerebral portals. At the end of the period of immunization the rabbits were bled and the serums were tested to determine their abilities to neutralize one strain of virus (B. A. C.'s cutaneous strain). Immunized animals were then challenged to determine their resistance to the heterologous strains, particularly to the HF strain of the virus of herpes simplex. The immunized animals received 0.25 cc. of a 1:50 or 1:100 dilution of virus; the control rabbits received dilutions of virus ranging from 1:100 to 1:5,000. All rabbits were challenged by the intracerebral portal and then observed for at least six weeks.

Results; Nature of the Infectious Agents.—Initial Passage: The histories of the isolation of four human strains follow:

(*a*) When vesicular exudate from dermal lesions of patient B. A. C. was diluted with 0.5 cc. of sterile distilled water and inoculated on the scarified cornea of rabbit 1, keratoconjunctivitis appeared forty-eight hours later and suppurative conjunctivitis on the third day. Although this reaction had subsided on the sixth day, the

7. Alundum is crystalline aluminum oxide, made by the Norton Company, Worcester, Mass., and used because of its excellent "cutting" qualities.

8. All inoculations were carried out while the animals were under full ether anesthesia.

9. Macchiavello, A.: A Technique for the Staining of Rickettsiae, cited by Zinsser, H., in Virus and Rickettsial Diseases: A Symposium Held at the Harvard School of Public Health, 1939, Cambridge, Mass., Harvard University Press, 1940, p. 896.

10. The CFW strain of Swiss mice, obtained from the Carworth Farms, Inc., New York, was employed in these tests.

rabbit manifested a temperature of 106 F., circled toward the affected side and became ataxic and tremulous. No definite convulsive seizures were seen. The rabbit was killed on the ninth day (fig. 7).

(*b*) A 10 per cent aqueous suspension of brain tissue from patient B. A. C. was inoculated intracerebrally into rabbit 4. Forty-eight hours later the rabbit had a temperature of 106 F. Thereafter the temperature

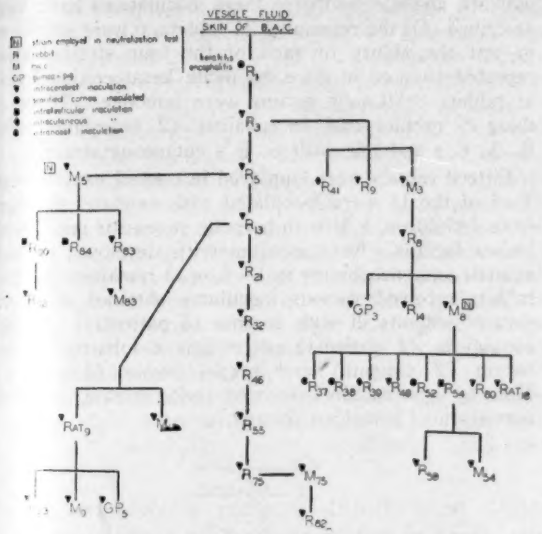

Fig. 7.—Chart of the serial passage of an infectious agent obtained from the vesicular fluid of patient B. A. C. in rodents.

dropped slowly to 104 F. until the seventh day, when it rose again to 106 F. and convulsive seizures were apparent. The rabbit was killed then to provide material for further passage.

Rabbit 4 was inoculated on March 11, 1942. Fractions of the inoculum which it received (maintained at —76 C.) produced encephalitis in a total of 6 rabbits; the last, rabbit 106, inoculated on Jan. 16, 1943, subsequently had encephalitis and died. The same material was apparently inert when tested in rabbit 115 on March 18, 1943. The original emulsions of cerebral tissue from patient B. A. C., therefore, contained an agent which was capable of provoking fatal encephalitis in rabbits ten months after storage and which withstood repeated thawing and freezing (fig. 8).

(*c*) Vesicular exudate from the dermal lesions of patient F. H. E. was diluted with 0.5 cc. of sterile distilled water and inoculated on the scarified cornea of rabbit 17. Vesicular keratitis was evidenced forty-eight hours later; the conjunctivas were involved on the third day. Although this animal had mild fever (temperature 104.5 F. for two days) no manifest disease of the central nervous system appeared. It was killed on the ninth day. Scrapings from the cornea of the affected eye and tissue from the brain of this rabbit were inoculated intracerebrally into 2 other rabbits. The rabbit inoculated with corneal scrapings later had encephalitis.

(*d*) Vesicular exudate from dermal lesions of patient S. F. was diluted with 4.0 cc. of distilled water. This suspension was divided into 2 parts; 0.5 cc. was used as a crude extract for immediate inoculation on the scarified corneas of rabbits, and the remaining 3.5 cc. was filtered through a small Berkefeld "N" candle.

Keratitis developed in 3 rabbits (R131, R139 and R141) inoculated on the scarified cornea with crude extract (fig. 9) within eighteen to twenty-four hours after inoculation and mild conjunctivitis eight to twelve hours later. The keratoconjunctivitis became purulent. After a week of fever (temperatures ranging from 104.2 to 105.5 F.) the animals recovered. All showed residual corneal opacities.

For control inoculations the crude extract was cultured and the bacterial growth (staphylococci and hemolytic streptococci) suspended in 4 cc. of saline solution. This suspension was inoculated on the scarified cornea of the other eye of each of the same 3 rabbits. In striking contrast to the results in the former tests, none of these evidenced ocular disease.

The filtrate of the vesicular fluid was bacteriologically sterile. When it was inoculated into a rabbit's brain encephalitis was produced seven days later (R140 in fig. 9).

Serial Transmission of the Infectious Agent in Rabbits: The previous tests indicated that the infectious agent isolated from each of the 3 sick infants was capable of causing encephalitis in rabbits. Furthermore, each of the four strains adapted to rabbits could be passed by brain to brain transfer in series in these animals (figs. 7, 8 9 and 10).

The cutaneous strain obtained from B. A. C. was the first isolated and has been studied, for purposes of orientation, in somewhat greater detail than have the others. This strain has proved to be highly virulent. The rabbit-adapted strain was transferred in series and caused encephalitis of fatal issue in rabbits through eight generations of passage.

The remaining three strains, B. A. C.'s cerebral strain and F. H. E.'s and S. F.'s cutaneous strains, could also be passed from rabbit to rabbit. Each of these strains has been through six or eight generations of transfer.

Description of the Disease Caused by the Infectious Agents in Rabbits.—(*a*) Intracerebral Inoculation of Virus: There were some differences among the four strains in their abilities to cause fatal encephalitis, particularly after intra-

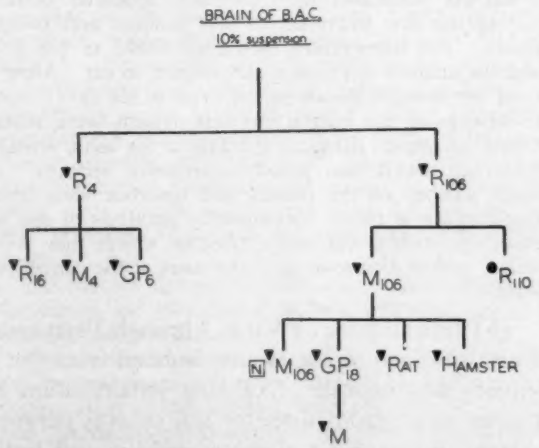

Fig. 8.—Chart of the passage of an infectious agent obtained from the brain of patient B. A. C. in rodents. The legends are the same as in fig. 7.

cerebral inoculation of rabbit-adapted strains. B. A. C.'s cutaneous and cerebral strains almost invariably caused encephalitis of fatal issue; F. H. E.'s strain caused a fatal outcome in 10 of 15 rabbits, and S. F.'s strain killed half of the rabbits only.

When each of the rabbit-adapted strains was established in the brains of other rodents, mice, rats and guinea pigs, and returned to the brains of rabbits an overwhelming infection resulted, terminating in death in forty-eight to seventy-two hours, rarely less. Moreover, strains adapted to small rodents, particularly to Swiss mice,

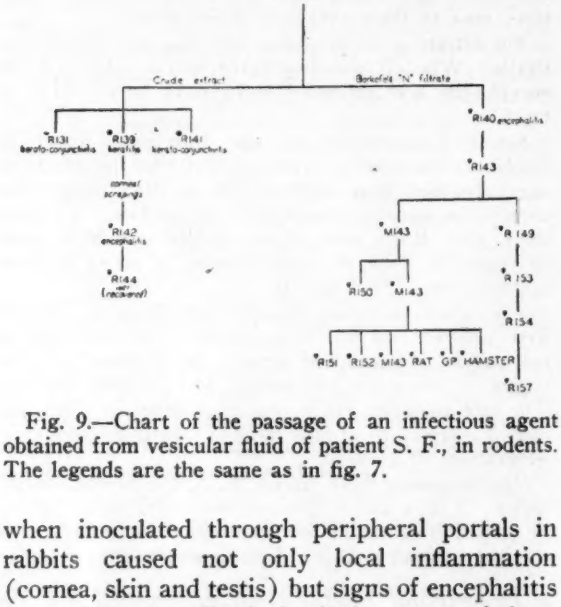

Fig. 9.—Chart of the passage of an infectious agent obtained from vesicular fluid of patient S. F., in rodents. The legends are the same as in fig. 7.

when inoculated through peripheral portals in rabbits caused not only local inflammation (cornea, skin and testis) but signs of encephalitis or myelitis as well. A detailed account of these tests will be considered later.

A summary of the clinical disease in rabbits follows:

Rabbits inoculated intracerebrally appeared healthy during the first thirty-six to one hundred and twenty hours. The temperature then rose (104.5 to 108 F.), and the animals were quiet and refused to eat. After a brief but variable febrile period (two to six days) signs of disease of the central nervous system were manifested: tremors, salivation, grinding of the teeth, urinary retention, ataxia and usually convulsive seizures. A large number of the rabbits had diarrhea and, later, incontinence of feces. Occasionally paralysis of one or more extremities was seen. Usually, unless they were killed, rabbits died soon after the onset of the convulsive state.

(*b*) Inoculations ov Virus Through Peripheral Portals: Each of the strains isolated from the 3 infants was capable of causing inflammation in tissues apart from those of the central nervous system, for example, the cornea, skin and testis in rabbits. The results show that after extraneural inoculation of virus the agent may extend from the locus of inoculation into the central nervous system, thereby causing demonstrable clinical symptoms and pathologic changes.

In relation to inoculation by the corneal portal two problems required consideration. 1. Were the animal-adapted strains able to cause keratoconjunctivitis identical to that following the initial passage of human inoculums? 2. Were the agents in question widespread in distribution and accidentally present?

To answer these questions tests were accomplished as follows:

Twenty-six rabbits were given corneal inoculations. Five of these rabbits were used in testing inoculum from patients, and the results of these inoculations have been described. Of the remaining 21 rabbits, 6 were employed to test the ability of each of the four strains, after repeated passage in mice, to incite keratoconjunctivitis in rabbits. All four strains were infective. Three of these 6 rabbits had encephalitis (2 inoculated with B. A. C.'s and one with S. F.'s cutaneous strain).

Fifteen rabbits were employed in control experiments. Two of the 15 were inoculated with exudates obtained from 2 children, 1 ill with herpetic stomatitis and 1 with herpes facialis. Keratoconjunctivitis developed in both animals and encephalitis in 1. The 13 remaining control rabbits received various inoculums obtained from the skin of patients ill with eczema (6 patients), impetigo contagiosa (5 patients), dermatitis exfoliativa neonatorum (2 patients) and herpes zoster (1 patient). None of these rabbits evidenced ocular disease, and their temperatures remained normal.

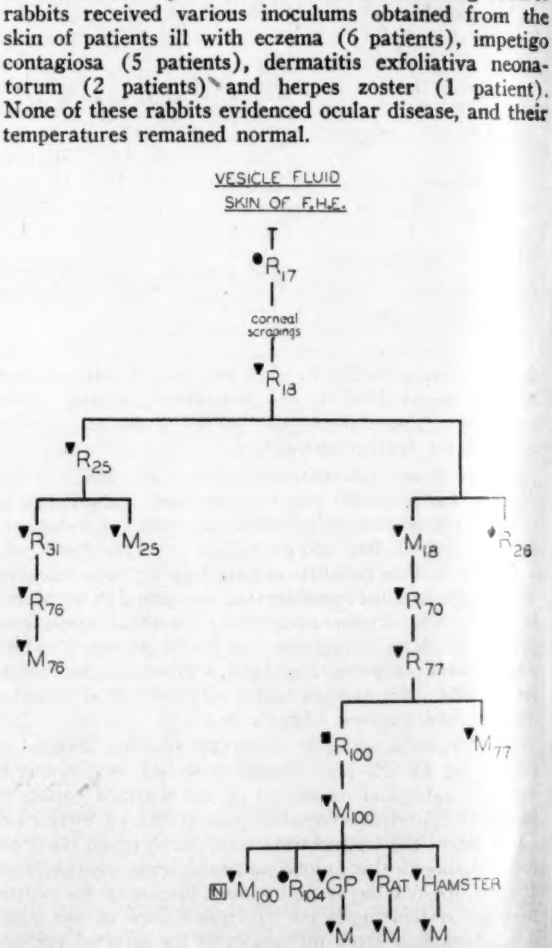

Fig. 10.—Chart of the passage of an infectious agent obtained from the vesicular fluid of patient F. H. E. The legends are the same as in figure 7.

Intradermal inoculation was used on 14 rabbits.

The inoculum consisted of virus adapted to mice or rabbits from three of our strains (B. A. C.'s cutaneous and cerebral strains and F. H. E.'s cutaneous strain) and the HF strain of herpes simplex virus. Tissue from the brains of normal mice and rabbits was used

for control inoculations. Of the 14 rabbits, none showed lesions similar to those seen in the patients in question. All showed some dermal reaction. In 8 of the rabbits the reaction caused by the test material was hardly greater than that at the site of the control injection. Four rabbits showed erythema with ulcerative, necrotic pustules, and in 1 a severe vesiculating and, later, ulcerating dermatitis appeared (Note: test virus was propagated in the testis). Eight rabbits showed fever, with temperatures between 105 and 106.5 F. Four of the 14 rabbits became paralyzed (2 inoculated with B. A. C.'s and 2 with F. H. E.'s cutaneous strain). There was no apparent relationship between the severity of the dermal insult and the appearance of myelitis.

Each of three strains was employed in 10 tests with intratesticular inoculation. Mouse-adapted strains produced orchitis in rabbits regularly. In 1 of the rabbits encephalitis developed after inoculation of its testis with B. A. C.'s cutaneous strain. Brain tissue from this rabbit (rabbit 90, fig. 7) caused encephalitis when inoculated intracerebrally into another. Testicular emulsion prepared from testes infected with each of the strains (twenty-four to forty-eight hours after inoculation) caused encephalitis also in rabbits and Swiss mice (1:1,000 dilution or more).

B. A. C.'s cutaneous strain was the only one inoculated intranasally. After an incubation period of eight days, signs of encephalitis were manifested, and the animal died.

Experimentally Induced Infection in Other Animals.—Each of the four strains of virus having been adapted to rabbits caused encephalomyelitis in Swiss mice, rats, guinea pigs and hamsters but not in rhesus monkeys (Macaca mulatta), ferrets or a dog after intracerebral inoculation. The passage and the history of the strain employed are illustrated schematically in figures 7, 8, 9 and 10.

Young Swiss mice inoculated with a 10 per cent suspension of brain of an infected rabbit (each of four strains) became ill after an incubation period varying from two to four days. Their coats were rough, and they were anorexic and sat humped in their cages; frequently they were hyperkinetic to ordinary stimuli. Sometimes they were agitated and moved or circled continuously about their cages. Subsequently convulsions occurred, and the mice died. Rarely, flaccid paralysis of the rear extremities was present before death.

Guinea pigs, hamsters and rats inoculated intracerebrally with each of four strains adapted to rabbits or mice became sick (temperature 102 to 105 F. in rats and 103.5 to 105.5 F. in guinea pigs). They had tremors, were ataxic and frequently had convulsions.

The small rodents that had encephalitis or symptoms suggestive of it were killed, and an emulsion of the brain of each of these animals was tested by intracerebral passage in Swiss mice and rabbits. Invariably encephalitis occurred in these animals.

Two young adult monkeys were inoculated intracerebrally also (B. A. C.'s M5 cutaneous and M106 cerebral strain). A mongrel dog was inoculated intracerebrally and a ferret intranasally with the M5 strain. None of these animals showed clinical or pathologic evidence of disease of the central nervous system.

Pathologic Picture.—The gross pathologic changes in all rabbits and other rodents which died or were killed were recorded. No pathologic changes were observed in the spleen, heart, liver and kidneys, regardless of the portal of inoculation. Visceral abnormalities noted in rabbits succumbing to encephalitis were a bladder greatly distended with urine and an empty, ballooned, atonic large intestine. Rarely, bronchopneumonia was evident in rabbits that died.

Central Nervous System: The gross pathologic changes consisted of (1) edema of the brain and meninges, (2) considerable congestion of the meningeal and subpial blood vessels and (3) ecchymoses in visible areas (0.05 mm. or smaller), best seen in the regions of the cerebral cortex and basal ganglions.

The microscopic changes produced by the virus in the central nervous system were characterized by (1) meningitis, (2) diffuse and sometimes focal encephalitis and, less constantly, (3) meningomyelitis. Eosinophilic intranuclear inclusion bodies[11] of the type described for herpes simplex, varicella, virus III disease and salivary gland disease of guinea pigs were present in the cells of the hippocampus, particularly in those comprising the cornu ammonis.

A serous meningitis involved the cortical surfaces of the brain and, to a less extent, the basal areas as well. The meningeal reaction was chiefly a mononuclear response, the infiltrate being composed of round cells, larger monocytic cells and, occasionally, polymorphonuclear leukocytes. Congested blood vessels of the leptomeninges were cuffed by numerous round cells, as were the vascular channels penetrating the cortical tissue from the meninges.

The encephalitis was characterized by diffuse or localized disorganization of the cerebral cells and matrix, particularly in the cortical areas. Most of the cytologic structure was distorted; the cells were swollen and their nuclei pyknotic. Cellular destruction was evident also in the basal ganglions, hippocampus and pons. Neuronophagia and neuronophagia were evident in areas adjacent to blood vessels. Nuclear inclusions like those present in herpes simplex infection were most conspicuous in the area of the cornu ammonis. Guarnieri bodies and Negri bodies were not demonstrated. Perivascular cuffing with round cells was extensive unless the incubation period was less than seventy-six hours, in which case relatively little perivascular reaction was noted. How much of this particular reaction resulted from past infection with Encephalitozoon cuniculi is not known[12]; nevertheless, other more specific cellular reactions demonstrate that this protozoon was not the responsible encephalitic agent.

The choroid plexus of rabbits with encephalitis, except for edema and vacuolation of cells, evidenced no acute inflammatory reaction.

The meningomyelitis consisted of (*a*) infiltration of the leptomeninges by round cells, (*b*) swelling and degeneration of the anterior horn cells in the cervical and lumbar segments of the cord and (*c*) infiltration by round cells of the small blood vessels of the meninges and the cord proper. No inclusion bodies were seen.

Ocular Tissue: In early lesions in the cornea (twenty-four to forty-eight hours) the epithelial cells were swollen and eosinophilic intranuclear inclusions

11. Dr. Ernest W. Goodpasture examined histologic sections obtained from the central nervous systems of the experimental animals.

12. Flexner, S., and Amoss, H. L.: Contributions to the Pathology of Experimental Virus Encephalitis, J. Exper. Med. **41**:357 (March) 1925.

were evident. As the inflammatory reaction progressed (four to ten days) the corneal epithelium evidenced ulceration, sometimes minimal but with distinct cellular destruction and at other times so extensive as to leave barely intact a few discrete epithelial landmarks. Numerous eosinophilic cells and small plasma cells infiltrated the corneal epithelium and the anterior chamber. Guarnieri bodies were not seen.

Adrenal Glands: These were examined occasionally, usually from rabbits succumbing to encephalitis. There was little evidence of destruction of tissue, and no inclusion bodies were seen.

Testes: The testis into which the virus was injected, regardless of the strain used, evidenced disorganization of the interstitial and parenchymal tissue. The inflammatory reaction consisted chiefly of edema and infiltration of all parts of the testis with large mononuclear cells. Although the testes were usually removed forty-eight to ninety-six hours after inoculation, we could not demonstrate inclusion bodies in their cells. Testes from apparently normal rabbits were obtained for comparative observations.

Tissues obtained from the central nervous system of other rodents manifesting signs of encephalitis showed histologic changes similar to those described as occurring in rabbits, except that inclusion bodies were not always readily seen.

Properties of the Infectious Agent.—Three strains, F. H. E.'s cutaneous and B. A. C.'s cutaneous and cerebral, were tested for filtrability with mouse-adapted virus. Each strain passed through Berkefeld "N" candles and through Pasteur-Chamberland L_3 candles but not through L_5 candles.

In the brains of rabbits and mice infected with any of the strains tested, the virus remained active in 50 per cent glycerin for at least eighty days. Material stored for longer periods was not tested.

Cultures made from meninges and brains of infected animals obtained at necropsy were almost uniformly without bacterial growth when incubated on ordinary blood agar plates. Emulsions prepared from infected tissues, such as brain or testis, were always bacteriologically sterile. Aerobic and anaerobic cultivation of extracts of infectious tissue on a variety of mediums (defined earlier) demonstrated no visible bacterial growth.

The preceding studies indicate that the infectious agents in question are filtrable viruses. The responses evoked by the agents in animals, particularly the pathologic changes resulting from infection by them, indicate that the 4 clinical strains of the agent are closely related to each other and that they are more closely related to the virus herpes simplex than to any other filtrable virus.

IMMUNOLOGIC STUDIES

The next step was to seek evidence linking the infectious agents isolated in the laboratory to the cutaneous eruptions occurring in the 3 infants. Moreover, further studies were necessary to clarify the relationship of each of the four strains to the virus of herpes simplex. To these ends two immunologic methods were employed, neutralization tests and resistance tests.

Neutralization Tests.—Tests showed that circulating antibodies effectively neutralizing the four strains of virus were present in 2 of the 3 infants convalescing from the cutaneous eruption in question. Because serum was not obtained at the proper intervals a rise in the antibody titer was not demonstrated in either of the 2 infants (although observations were made on the level of the antibodies until they disappeared in 1 of the cases).

In order to evaluate these observations, and because previous workers had emphasized that antibodies capable of inactivating the virus of herpes simplex may be present in many adults [13] and to a less extent in children,[14] it was necessary to know whether antibodies capable of neutralizing one of the four related strains under consideration were usually present in normal human serum. In particular, the effort was made to establish a base line for antibody titer in children less than 3 years and more than 6 months of age in order to evaluate significant deviations from apparently normal titers of neutralizing antibodies. The term "significant" has been added because it was soon apparent that some children with no history of previous herpetic infection had antibodies in their serum capable of neutralizing ten to one hundred times the dose of virus lethal for a mouse. Hence the criteria adapted to indicate the presence of significant levels of antibodies require that at least one hundred and preferably one thousand times the minimum lethal dose of virus for a mouse be neutralized unquestionably by the serum tested.

Data on the infectivity of each of the four strains adapted to mice follow:

Brain to brain passage in mice was accomplished easily, but the behavior of the four strains in respect to the end point of titration was somewhat irregular. The best end points were obtained with material from the brains of mice used in the first three generations of

13. (*a*) Zinsser, H., and Tang, F.: Further Experiments on the Agent of Herpes, J. Immunol. **17**:343 (Oct.) 1929. (*b*) Andrewes, C. H., and Carmichael, E. A.: A Note on the Presence of Antibodies to Herpes Virus in Post-Encephalitic and Other Human Sera, Lancet **1**:857 (April 19) 1930. (*c*) Burnet, F. M., and Lush, D.: Herpes Simplex: Studies on the Antibody Content of Human Sera, ibid. **1**:629 (March 18) 1939.

14. Weyer, E. R.: Herpes Antiviral Substances: Distribution in Various Age Groups and Apparent Absence in Individuals Susceptible to Poliomyelitis, Proc. Soc. Exper. Biol. & Med. **30**:309 (Dec.) 1932.

passage. Thereafter, the virus was lethal to mice in lower dilutions (a ten to one hundred fold decrement). As a result of this observation suspensions of infected brain tissue from the first or second passage were maintained in the frozen state and later passed to new mice for a source of virus for use in the neutralization tests.

The comparative and selective activity of each mouse-adapted strain of virus was tested. B. A. C.'s cutaneous strain had a fairly clearcut end point when titrated in a dilution of 1:100,000, B. A. C.'s cerebral strain in a dilution of 1:10,000, F. H. E.'s cutaneous strain in a dilution of 1:10,000 and S. F.'s cutaneous strain in a dilution of 1:100,000. The HF strain of the virus of herpes simplex had an end point in a dilution beyond 1:100,000. B. A. C.'s cerebral strain was exceptional in that it was impossible to keep it titered at the maximal end point in the conduct of the neutralization test. We are not in a position to explain this variation, although we have checked most of the factors, other than variations in the virus, which may have caused it.

Tests of the neutralization of the four strains of virus (*a*) by patient's serum (convalescent) and control human serum (infant's and children's) and (*b*) by immune rabbit serum were made.

Neutralization of Virus by Human Serum: Serum obtained from patient F. H. E. effectively neutralized each of the four strains of virus (F. H. E.'s and B. A. C.'s strains and the HF strain of herpes simplex virus). The results appear in table 4. From the data presented it would appear that in this case circulating antibodies capable of inactivating one or another of the four strains persisted for at least seven and possibly nine months after the onset of the patient's illness and then disappeared. The disappearance of neutralizing antibodies at this particular time is important, inasmuch as it provides somewhat firmer evidence than heretofore seen that the virus is related to the illness which the infant had.

These results provide evidence of an immunologic relationship between the four strains of virus in question. The relationship to the virus of herpes simplex is evidenced by the neutralization of the HF strain of herpes simplex virus by F. H. E.'s serum, and also by the neutralization of the M5 strain, obtained from cutaneous lesions of patient B. A. C., by serum obtained from a patient (D. E. S., table 4) who had herpes facialis.

D. E. S., a boy 12 years of age, was convalescent from pneumococcic pneumonia and herpes facialis. Fluid from this patient's herpetic vesicles inoculated on the scarified cornea of a rabbit caused keratoconjunctivitis and encephalitis. Serum obtained from D. E. S. twelve days after the appearance of herpetic lesions effectively neutralized the M5 strain.

In the testing of serum from patient S. F. an attempt was made to demonstrate a rise in the titer of neutralizing antibodies. Two tests have been completed with serum obtained on the eighth day (when lesions were crusting) and on the twenty-third day (when new vesicles were appearing) of illness. The heterologous M5 strain (B. A. C., cutaneous) was used as virus, for when these tests were done the homologous strain had not been adapted to mice. The results appear in table 5. Appreciable amounts of circulating antibodies capable of inactivating the heterologous M5 strain were present on the eighth day. Serum obtained on the twenty-third day was not quite as effective in neutralizing the M5 strain as serum obtained earlier. Although the results are within the range of biologic error, it may be pointed out that when the last of these serums was tested a recrudescence of vesicles was occurring in the patient. The testing of serum obtained later in convalescence remains to be accomplished. The presence of a significant titer of neutralizing antibodies in the serum of S. F., which inactivated the M5 strain, indicates that the infectious agent (which has been isolated) associated with her illness was immunologically related to the strains obtained from the other 2 patients.

Neutralization of Virus by Serum from Infants and Children: The results of the neutralization tests with serum from 20 infants and children appear in tables 4 and 6. Of the 20 children, 3 afforded evidence of significant titers of neutralizing antibodies in their serum. Of these 3 children, 2 had illnesses which may serve to explain the presence of these antibodies; D. E. S., referred to previously (table 4), had had herpes facialis, and G. S. R., a microcephalic infant (table 6) ill with infected eczema, had a vesicular eruption on the palms and fingers a month before serum was obtained. The third child, J. A. B., was ill with infected eczema also, but, as far as is known, he did not have an illness like that of the patients from whom the strains studied were isolated.

The results of these tests do not demonstrate conclusively that the presence of neutralizing antibodies in the serum of the 3 patients whose cases are reported here resulted from infection by the virus isolated from them. Nevertheless, the data show that neutralizing antibodies capable of inactivating the strains isolated from them are present in human serum. Moreover, the presence of significant titers of neutralizing antibodies in human serum provides firm evidence of a relatively recent infection with a virus related to the strains isolated from our patients.

Neutralization of Virus by Immune Rabbit Serum: Serum obtained from rabbits at the end

TABLE 4.—*Capacity of F. H. E.'s Serum to Neutralize His Own Strain of Virus, B. A. C.'s Cutaneous and Cerebral Strains and the HF Strain of the Virus of Herpes Simplex, Compared with Capacity of Serum from Human and Animal Controls*

Strain* of Virus	Source of Serum	Age of Patient	Date Serum Obtained	Date of Test	Fate of Mice Inoculated with Various Dilutions of Virus						Results
					10^{-1}	10^{-2}	10^{-3}	10^{-4}	10^{-5}	10^{-6}	
F. H. E. (M100)	Normal rabbit	.....	.....	2/20/43	4/4†	4/4	4/4	4/4	1/4	...	Negative
F. H. E. (M100)	R. T. S.	24 mo.	.....	2/20/43	4/4	4/4	3/4	2/4	2/4	...	Negative
F. H. E. (M100)	F. H. E.	23 mo.	7/17/42	2/20/43	1/4	0/4	0/4	0/4	0/4	...	Positive
B. A. C. (M5) cutaneous	Normal rabbit	.....	.....	12/ 4/42	5/5	5/5	5/5	4/5	4/5	2/5	Negative
B. A. C. (M5) cutaneous	S. A. R.	18 mo.	.....	12/ 4/42	5/5	5/5	4/5	4/5	3/5	...	Negative
B. A. C. (M5) cutaneous	F. H. E.	21 mo.	5/12/42	12/ 4/42	5/5	1/5	1/5	0/5	0/5	...	Positive
B. A. C. (M106) cerebral	Normal rabbit	.....	.....	2/28/43	4/4	4/4	3/4	1/4	1/4	0/4	Negative
B. A. C. (M106) cerebral	L. Y. N.	21 mo.	.....	2/28/43	4/4	3/4	0/4	0/4	0/4	...	Equivocal
B. A. C. (M106) cerebral	F. H. E.	25 mo.	9/22/42	2/28/43	2/4	1/4	0/4	0/4	0/4	...	Positive
HF (M4)	Normal rabbit	.....	.....	12/ 4/42	5/5	5/5	5/5	5/5	4/5	1/5	Negative
HF (M4)	S. A. R.	18 mo.	.....	12/ 4/42	5/5	5/5	5/5	5/5	3/4	..	Negative
HF (M4)	F. H. E.	21 mo.	5/12/42	12/ 4/42	5/5	2/5	1/5	1/5	0/5	...	Positive
B. A. C. (M5) cutaneous	Normal rabbit	.....	.....	4/20/43	4/4	4/4	4/4	4/4	3/4	2/4	Negative
B. A. C. (M5) cutaneous	I. N. G.	14 mo.	.....	4/20/43	4/4	4/4	4/4	4/4	4/4	...	Negative
B. A. C. (M5) cutaneous	F. H. E.	28 mo.	12/ 7/42	4/20/43	4/4	4/4	4/4	4/4	4/4	...	Negative
B. A. C. (M5) cutaneous	D. E. S.‡	9 yr.	1/21/43	4/20/43	2/3	1/4	1/4	0/4	0/4	...	Positive

* The histories of the strains (in parenthesis) are outlined in figures 7, 8 and 9.
† Denominator = number of mice inoculated; numerator = number of deaths.
‡ Patient with herpes facialis; onset of illness 1/9/43; positive results obtained from inoculation of vesicular fluid in the scarified cornea of a rabbit.

TABLE 5.—*Capacity of S. F.'s Serum to Neutralize B. A. C.'s M5 Strain of Virus* **

Strain of Virus	Source of Serum	Age of Patient	Day Since Onset of Disease	Date of Test	Fate of Mice Inoculated with Various Dilutions of Virus						Results
					10^{-1}	10^{-2}	10^{-3}	10^{-4}	10^{-5}	10^{-6}	
B. A. C. (M5) cutaneous	I. N. G.†	14 mo.	.....	6/15/43	4/4	4/4	4/4	4/4	2/4	0/4	Negative
B. A. C. (M5) cutaneous	S. F.	8 mo.	8	6/15/43	4/4	2/4	1/4	0/4	...	...	Positive
B. A. C. (M5) cutaneous	S. F.	8 mo.	23	6/15/43	4/4	3/4	3/4	0/4	...	...	Positive

* The symbols designating the history of the strain employed and the fate of mice inoculated have been defined in table 4.
† Serum known not to contain the virus of herpes simplex.

of a period of immunization and preceding challenge inoculation with heterologous strains of virus was tested to show, if possible, the presence of neutralizing antibodies and the cross neutralization of the strains of virus in question (table 7).

Rabbits were immunized with three of the strains isolated (B. A. C.'s and F. H. E.'s strains) and with the HF strain of the virus of herpes simplex. The portals of inoculation are listed in table 8. Antiserum obtained from rabbits inoculated with each of the four strains neutralized the M5 strain about equally well (table 7). The results were somewhat more definite with serum from animals immunized with the homologous strain, but not significantly so. Normal rabbit serum has never neutralized any of the strains with which my associates and I have been concerned.

Resistance Tests.—Rabbits immunized respectively with three of our clinical strains (not including S. F.'s) and with the HF strain of herpes simplex were tested to determine their resistance to intracerebral inoculation of the challenge strain of virus, generally the HF strain of the virus of herpes simplex.

The immunization of rabbits was accomplished by repeated inoculation of potent strains of virus through different portals for varying periods (table 8). In preliminary experiments it was observed that rabbits that manifested fever (temperature 105 F. or higher) after extraneural inoculation with virus were more resistant to challenge intracerebral inoculation than animals that did not. We took this to mean that the virus was provoking a generalized infection and presumably invading the central nervous system, although signs of such invasion were not always seen. Of the rabbits that did not show fever, many died of encephalitis when challenged intracerebrally by the strain employed in immunizing them. Therefore, a number of the rabbits to be used in tests of resistance to the virus of herpes simplex (table 8) were challenged first by intracerebral inoculation of homologous virus. Those that survived were later (at least a month afterward) challenged again with a heterologous strain, usually the HF strain of herpes simplex virus. This procedure, it may be pointed out, is not a good one, in that it has been shown that the presence of one neurotropic virus in the brain of the susceptible animal may interfere with the subsequent action of another.[15]

15. Morgan, I. M.; Schlesinger, R. W., and Olitsky, P. K.: Induced Resistance of the Central Nervous System to Experimental Infection with Equine Encephalomyelitis Virus, J. Exper. Med. **76**:357 (Oct.) 1942.

TABLE 6.—*Neutralization of Two Strains of Virus by Serums Obtained from Fifteen Control Infants and from Normal Rabbits* **

Strain of Virus	Source of Serum	Age of Patient	Disease Present	Date of Test	Fate of Mice Inoculated with Various Dilutions of Virus					Results
					10^{-1}	10^{-2}	10^{-3}	10^{-4}	10^{-5}	
HF (M4)†	Rabbit	.....	.....	12/ 4/42	5/5	5/5	5/5	5/5	4/5	Negative
HF (M4)	C. N. T.	3 yr.	None	12/ 4/42	3/3	5/5	4/4	3/4	...	Negative
B. A. C. (M5) cutaneous	C. N. T.	3 yr.	None	4/19/43	4/4	4/4	3/4	3/4	3/4	Negative
B. A. C. (M5) cutaneous	Rabbit	.....	None	4/19/43	4/4	4/4	4/4	4/4	3/4	Negative
B. A. C. (M5) cutaneous	B. S. R.	14 mo.	Infected eczema and microcephaly	4/19/43	4/4	2/4	0/4	0/4	0/4	Positive
B. A. C. (M5) cutaneous	P. R. N.	11 mo.	None	4/19/43	4/4	4/4	4/4	1/4	0/4	Negative
B. A. C. (M5) cutaneous	P. L. D.	8 mo.	Asthmatic bronchitis	4/19/43	4/4	4/4	4/4	2/4	0/4	Negative
B. A. C. (M5) cutaneous	F. L. G.	29 mo.	None	4/19/43	4/4	4/4	4/4	2/4	0/4	Negative
B. A. C. (M5) cutaneous	Rabbit	.....	.....	4/19/43	4/4	4/4	4/4	4/4	3/4	Negative
B. A. C. (M5) cutaneous	G. D. Y.	14 mo.	Sickle cell anemia	4/19/43	4/4	4/4	4/4	2/4	...	Negative
B. A. C. (M5) cutaneous	A. D. M.	3 yr.	None	4/19/43	4/4	4/4	4/4	4/4	...	Negative
B. A. C. (M5) cutaneous	M. C. O.	20 mo.	None	4/19/43	4/4	4/4	4/4	4/4	...	Negative
B. A. C. (M5) cutaneous	Rabbit	.....	.....	4/19/43	4/4	4/4	4/4	4/4	3/4	Negative
B. A. C. (M5) cutaneous	N. X. N.	6 mo.	Polycystic kidney	4/19/43	4/4	4/4	3/4	1/4	0/4	Equivocal
B. A. C. (M5) cutaneous	E. W. N.	29 mo.	None	4/19/43	4/4	4/4	4/4	2/4	...	Negative
B. A. C. (M5) cutaneous	D. E. L.	6 mo.	Convulsive seizures	4/19/43	4/4	4/4	2/4	2/4	1/4	Equivocal
B. A. C. (M5) cutaneous	N. S. N.	1 yr.	None	4/19/43	4/4	4/4	4/4	0/4	0/4	Negative
B. A. C. (M5) cutaneous	Rabbit	.....	.....	5/20/43	4/4	4/4	4/4	4/4	2/4	Negative
B. A. C. (M5) cutaneous	J. A. B.	8 mo.	Infected eczema	5/20/43	4/4	3/4	1/4	1/4	0/4	Positive
B. A. C. (M5) cutaneous	A. E. C.	6 mo.	Infected eczema	5/20/43	4/4	4/4	3/4	2/4	...	Negative
B. A. C. (M5) cutaneous	M. H. H.	6 mo.	Infected eczema	5/20/43	4/4	4/4	3/4	2/4	...	Negative

* The history of the strain employed and the fate of mice used in these tests are defined in table 4.
† Herpes simplex virus; our fourth generation of passage.

TABLE 7.—*Neutralization of B. A. C.'s M5 Strain by Hyperimmune Serum from Rabbits Inoculated with One of Four Strains of Virus* **

Strain of Virus	Source of Serum	Strain Employed in Immunization	Date of Test	Fate of Mice Inoculated with Various Dilutions of Virus					Results
				10^{-1}	10^{-2}	10^{-3}	10^{-4}	10^{-5}	
B. A. C. (M5) cutaneous	Normal rabbit	None	6/2/43	4/4	4/4	4/4	3/4	0/4	Negative
B. A. C. (M5) cutaneous	Rabbit 100 †	F. H. E.'s cutaneous strain	6/2/43	4/4	3/4	0/3	0/4	...	Positive
B. A. C. (M5) cutaneous	Rabbit 107 †	Herpes simplex, HF	6/2/43	4/4	4/4	1/4	1/5	...	Positive
B. A. C. (M5) cutaneous	Rabbit 109 †	B. A. C.'s cutaneous strain	6/2/43	4/4	2/4	1/4	1/4	...	Positive
B. A. C. (M5) cutaneous	Rabbit 122 †	B. A. C.'s cerebral strain	6/2/43	4/4	2/4	0/4	0/4	...	Positive

* The symbols designating the history of the strain employed and the fate of mice used in these tests have been defined in table 4.
† Serum was obtained from rabbits a week prior to challenge inoculation (table 8) with HF strain of herpes simplex virus.

In regard to this, it has been stated that the virus of herpes simplex may remain dormant in immunized rabbits for as long as six months and then cause encephalitis.[16]

Two series of tests were completed. The results appear in table 8.

In the first series all except 1 of 5 rabbits were protected. The 5 rabbits represented immunization with two strains, B. A. C.'s and F. H. E.'s cutaneous strains. The virus used for the challenge inoculation was the HF strain of herpes simplex virus. One rabbit immunized with B. A. C.'s cutaneous strain died of encephalitis with symptoms similar to those described[17] as occurring in animals partially immune to herpes simplex, namely, fever, lethargy, somnolence, prostration and death. The remaining rabbits were resistant and remained healthy.

In the second series of tests, 10 rabbits were each immunized with one of our three strains or with the HF strain of the virus of herpes simplex. The animals immunized with our strains were challenged with the HF strain; the rabbit immunized with the HF strain was challenged with B. A. C.'s cerebral strain. Three rabbits died of encephalitis, 1 on the seventh day

TABLE 8.—*Resistance of Immunized Rabbits to HF Strain of the Virus of Herpes Simplex* *

Immunization						Tests of Resistance						
Strain of Virus	Source of Strain	Portals ‡ of Inoculation	Amount Inoculated (10^{-1}) Cc.	Period of Immunization †	Temperature after Immunizing Inoculations	Strain	Portal ‡	Amount Cc.	Dilution	Date	Rabbit No.	Results
B. A. C. cutaneous	R3	id-ic	10.0	9 mo.	104.5 F.	HF	ic	0.25	1:100	1/4/43	12	Protected
B. A. C. cutaneous	M8	it-id	6.5	4 mo.	106.0	HF	ic	0.25	1:100	1/4/43	54	Protected
B. A. C. cutaneous	M5	id	8.5	3 mo.	104.3	HF	ic	0.25	1:100	1/4/43	89	Paralyzed; chronic encephalitis
B. A. C. cutaneous	R90	id-it	2.0	2 mo.	104.5	HF	ic	0.25	1:100	1/4/43	93	Protected
F. H. E. cutaneous	R18	id	4.5	7 mo.	105.5	HF	ic	0.25	1:100	1/4/43	40	Protected
None	.....	....	....	.....	.....	HF	ic	0.25	1:100	1/4/43	95	Encephalitis; died on fifth day
None	.....	....	....	.....	.....	HF	ic	0.25	1:100	1/4/43	96	Encephalitis; died on sixth day
None	.....	....	....	.....	.....	HF	ic	0.25	1:100	1/4/43	97	Encephalitis; died on sixth day
None	.....	....	....	.....	.....	HF	ic	0.25	1:100	1/4/43	98	Encephalitis; died on fifth day
None	.....	....	....	.....	.....	HF	ic	0.25	1:100	1/4/43	99	Encephalitis; died on sixth day
F. H. E. cutaneous	R77	it-id-ip-ic	15.0	6 mo.	105.2	HF	ic	0.25	1:50	6/1/43	100	Protected
F. H. E. cutaneous	R70	id-ip-ic	11.5	3 mo.	Normal	HF	ic	0.25	1:50	6/1/43	118	Encephalitis (late); died on thirty-third day
F. H. E. cutaneous	R70	id-ip-ic	11.5	3 mo.	Normal	HF	ic	0.25	1:50	6/1/43	119	Encephalitis; died on seventh day
B. A. C. cutaneous	M8	id-ip-ic	19.0	4 mo.	Normal	HF	ic	0.25	1:50	6/1/43	109	Protected
B. A. C. cerebral	M106	it-id-ip-ic	7.0	3 mo.	106.0	HF	ic	0.25	1:50	6/1/43	112	Protected
B. A. C. cerebral	M106	it-id-ip ic	7.2	3 mo.	104.5	HF	ic	0.25	1:50	6/1/43	113	Protected
B. A. C. cerebral	M106	it-id-ip-ic	7.0	3 mo.	Normal	HF	ic	0.25	1:50	6/1/43	114	Protected
B. A. C. cerebral	R120	id-ip-ic	7.0	2 mo.	Normal	HF	ic	0.25	1:50	6/1/43	122	Protected
B. A. C. cerebral	R120	id-ip-ic	3.0	2 mo.	Normal	HF	ic	0.25	1:50	6/1/43	123	Encephalitis (late) died on thirty-first day
H. F.	R74	id-ip-ic	8.0	3 mo.	Normal	BAC	ic	0.25	1:100	6/1/43	138	Protected
None	.....	....	....	.....	.....	HF	ic	0.25	1:100	6/1/43	126	Encephalitis; died on fifth day
None	.....	....	....	.....	.....	HF	ic	0.25	1:100	6/1/43	133	Encephalitis; died on seventh day
None	.....	....	....	.....	.....	HF	ic	0.25	1:1,000	6/1/43	134	Encephalitis; died on sixth day
None	.....	....	....	.....	.....	HF	ic	0.25	1:1,000	6/1/43	135	Encephalitis; died on sixth day
None	.....	....	....	.....	.....	HF	ic	0.25	1:5,000	6/1/43	136	Encephalitis; died on eighth day
None	.....	....	....	.....	.....	HF	ic	0.25	1:5,000	6/1/43	137	Encephalitis; died on fourth day

* The source and history of the strains used in immunizing rabbits are outlined in figures 7, 8 and 9.
† The interval between the last immunizing inoculation and the test of resistance was one month.
‡ Portals of inoculation: ic = intracerebral, id = intradermal, ip = intraperitoneal and it = intratesticular.

16. Perdrau, J. R.: Persistence of Virus of Herpes in Rabbits Immunized with Living Virus, J. Path. & Bact. **47**:447 (Nov.) 1938.

17. Zinsser, H., and Tang, F.: Immunological Studies with Herpes Virus with a Consideration of the Herpes-Encephalitis Problem, J. Exper. Med. **44**:21, 1936.

(F. H. E.'s cutaneous strain), another on the thirty-first day (F. H. E.'s cutaneous strain) and the last (B. A. C.'s cerebral strain) on the thirty-third day following challenge inoculation with the HF strain of the virus of herpes simplex. The remaining rabbits were resistant and remained healthy.

These data conclude the evidence that three strains of virus isolated from the vesicles occurring in the course of an acute exanthem in 3 infants and a fourth strain, isolated from the brain of 1 of the infants, are each closely related to, if not identical with, the virus of herpes simplex, and that this virus was probably the causative agent of the illness manifested by each of the patients. Further evidence adduced from the data indicates that the virus isolated from the brain in the case which was fatal was identical with the virus recovered from the cutaneous lesions in that case.

COMMENT

In 1887 Kaposi [8] described a rare type of eruption occurring as a complication of infantile eczema. The clinical features of the disease as described by him are similar to those observed in the cases reported in this paper. This is best pointed out by quoting an abstract [8] from a later edition of his book (1889).

A very alarming complication of eczema infantum which has come under my observation in several cases is an acute outbreak of numerous vesicles, partly scattered, partly arranged in groups. The vesicles are as large as a lentil, filled with clear serum, and the majority are umbilicated. They look like varicella lesions, but undoubtedly do not belong to this class. The integument which has been attacked in this manner now appears still more swollen, even tense. The little patients have high fever (40 C. or more) and are very restless. The vesicles develop very acutely (sometimes overnight), in large numbers, and often continue to appear, in successive crops, for three or four days, or even a week. Those which appear first undergo desiccation, rupture, and expose the corium, or they become encrusted and fall off. The largest number of those varicella-like vesicles are found upon the already eczematous skin, but smaller groups appear upon the previously intact skin of the neighborhood, upon the forehead, ears, neck, and even the shoulder and arms.

The outcome of this peculiar affection always is, in the majority of instances favourable; the exposed surfaces are covered with new integument in two or three weeks. In many places pigment patches are left over, or even flat cicatrices. The previously existing eczema changes its character only in so far as it is influenced by local treatment. In a child of six months, under my observation, death occurred after eclamptic seizures on the sixth day of the disease, when the eruption was everywhere recovering and complete defervescence had ensued.

I am in doubt with regard to the proper term to apply to this varicella-like eruption which has never been seen by experienced pediatrists, while ten cases have come under my observation. Eczema herpetiforme seems to be a suitable appellation. I am also ignorant of its causation. I suspect, however, that we have to deal with local contagion by a fungus, which finds suitable soil in the epidermis that has been loosened by the eczema, and by its vegetating produces the peculiar eruption. The cases were all so rapid in their course that no opportunity for microscopical examination has hitherto been obtained. The threatening fever is not due to blood infection, but to local dermatitis.

Two years later Juliusberg [18] described what appears to be the same disease. He stated the belief that it was caused by pyogenic staphylococci, but remarked that the individual lesions resembled vaccination pustules described by Jenner. Since then the cause of "eczema herptiforme" and its precise relationship to eczema vaccinatum have been disputed. A number of bacteria and at least one of the filtrable viruses (vaccinia have been considered as etiologic agents. In recent years the search for a filtrable virus in the cutaneous lesions of patients with this disease has been reported.[19] In one of these studies [19b] Guarnieri bodies were seen in the corneal epithelium of rabbits, and in the other [19a] none were found. Other attempts failed entirely to reproduce a disease in animals.

It is not entirely clear, if the patients reported on had the disease described by Kaposi, as my associates and I believe they did, why the detection of the virus was so easy, whereas other investigators have failed to detect it. There may be several explanations for this. If the disease were caused by vaccinia virus, as some believe, positive results should be obtained by Paul's test, but the detection of this virus in patients with Kaposi's "eczema herptiforme" has been rarely accomplished, and when it has one cannot be certain that the eruption was not generalized vaccinia. Further, if the virus is to be isolated it is important that the inoculum should be obtained during the early vesicular stage of the disease (a relatively short period) and tested promptly.

Although the virus of herpes simplex has been suggested as the cause of Kaposi's "eczema herpetiformes," it has not been studied before. The evidence detailed in this study indicates that this particular virus, or one closely related to it, is presumably the causative agent of a disease indistinguishable from that described by Kaposi in 1889.

Finally, the isolation from brain tissue in a fatal case of a filtrable virus which is identical

18. Juliusberg, F.: Ueber Pustulosis acuta varioliformis, Arch. f. Dermat. u. Syph. **46**:21, 1898.

19. (*a*) Freud, P.: Ueber Pustulosis vacciniformis acuta, Monatschr. f. Kinderh. **51**:28, 1931. (*b*) Freund, H.: Zur Aetiologie der Pustulosis vacciniformis acuta (Kaposi-Juliusberg), Dermat. Wchnschr. **98**:52 (Jan. 13) 1934.

with the strain recovered from the skin of the same patient deserves comment. Although the evidence indicates that the virus was in the tissue of the brain and not in fluids bathing it, the absence of specific lesions in the central nervous system curtails any emphasis that might be given to the assumption that the virus was an encephalitic agent in this patient.

Nevertheless, recent evidence [20] suggests that the virus of herpes simplex may enter the central nervous system of human beings more frequently than has been thought previously, which is not surprising considering the ease with which certain strains of the virus reach the central nervous system in rodents.[21] The problem of herpetic encephalitis in human beings is still an open one, and it deserves closer scrutiny in relation to diseases of the central nervous system in infants and young children. It is in this group particularly that many obscure encephalopathies occur.

20. (*a*) Armstrong, C.: Herpes Simplex Virus Recovered from Spinal Fluid of Suspected Case of Lymphocytic Chorio-Meningitis, Pub. Health Rep. **58:16** (Jan. 1) 1943. (*b*) Smith, M. G., Lennette, E. H. and Reames, H. R.: Isolation of the Virus of Herpes Simplex and the Demonstration of Intranuclear Inclusions in a Case of Acute Encephalitis, Am. J. Path. **17:**55 (Jan.) 1941.

SUMMARY

An unusual eruption occurred in 3 infants chronically ill with eczema, characterized by a dermal reaction that passed through the stages of papule, vesicle, pustule and crust in seven to ten days. Strains of a filtrable virus isolated from the vesicular fluid of each of the 4 infants and from the brain of 1 of them at necropsy were identified as closely related to, if not identical with, the virus of herpes simplex.

The late Dr. James D. Trask pointed the way in these studies. Dr. Roswell D. Johnson, of the clinical staff of the pediatric service loaned photographs of 2 of the patients, and Mildred Fousek and Ruth B. Wenner gave valuable assistance in the study.

Yale University School of Medicine.

FACTORS INFLUENCING RETENTION OF NITROGEN AND CALCIUM IN PERIOD OF GROWTH

VI. THE CALCIUM AND VITAMIN D REQUIREMENTS OF THE OLDER CHILD

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DETROIT

Several reviews [1] stressing the paucity of data on the calcium and vitamin D requirements of older children suggested the desirability of bringing together a number of determinations over a significantly long term of the retention of these two items by older girls with varying intakes. Some of these data have been reported in connection with other problems, such as the influence of puberty [2] and the effect of estrogen,[3] and are merely summarized in table 1 as typical of the normal balance at puberty, without ingestion of additional vitamin D and without variation in the intake of calcium. Another group of cases in this age group is reported in detail to illustrate the effect of variation in the intake of vitamin D.

The comparative rarity of clinically recognizable rickets beyond infancy may account for the casual attitude of the average pediatrician toward adequate provision of calcium and vitamin D in the diets of older children, though it is logical to assume that other types of abnormality may be related to a deficiency of one or both of these substances in that age group. We have noted [4] that in the reinfection type of tuberculosis seen in adolescent children there is poor retention or no retention of nitrogen or calcium or both, though whether or not this condition is a cause or an effect is not wholly proved. Improved retentions and healing parallel each other, and the effecting of these increased retentions by high intakes of calcium and vitamin D has seemed to be a factor favorably influencing the healing. Data will be presented for the nitrogen and calcium balances of two girls who had the slipped upper femoral epiphysis of puberty, the underlying cause of which is unknown. It is significant that the highest incidence of this abnormality in girls is in the year preceding sexual maturity, when the speed of growth has become greatly accelerated. Whether or not hormonal effect is involved, the fact remains that one of these girls on what is considered an adequate intake had a negative balance for calcium, which could be converted into a positive balance by the use of supplemental vitamin D. The other girl had a calcium retention which was only a fraction of the usual amount and which was improved with vitamin D. Both of these patients were observed a year after the appearance of the slipping.

The daily allowances of calcium recommended by the Committee on Foods and Nutrition of the National Research Council are as follows:

	Age, Yr.	Calcium, Gm.
Girls.....	1 to 9	1.0
	10 to 12	1.2
	13 to 15	1.3
	16 to 20	1.0
Boys.....	13 to 15	1.4
	16 to 20	1.4

While superficially the relating of desirable intake to chronologic age would seem reasonable, a more logical approach would be to consider it a function of the rate of skeletal growth. There are a definite acceleration in the rate of skeletal growth in girls preceding menarche and an almost abrupt deceleration following menarche, indicating that the amount of calcium needed is thus becoming a function of physiologic rather than of chronologic age. The postmenarcheal deceleration is reflected in the diminished percentage utilization of calcium immediately following the menarche noted in the study on the influence of puberty.[3]

The amounts suggested by Leitch,[5] "assuming the maximum probable retention of fifty per cent

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1. (*a*) Jeans, P. C.: Handbook of Nutrition: The Feeding of Healthy Infants and Children, J. A. M. A. **120**:913-921 (Nov. 21) 1942. (*b*) Jeans, P. C., and Stearns, G.: The Effect of Vitamin D on Linear Growth in Infancy: Effect of Intakes Above 1,800 U. S. P. Units Daily, J. Pediat. **13**:730-740 (Nov.) 1938.

2. Johnston, J. A.: Factors Influencing Retention of Nitrogen and Calcium in Period of Growth: III. Puberty in the Normal Girl and in the Girl with the Minimal Reinfection Type of Tuberculosis, Am. J. Dis. Child. **59**:287-309 (Feb.) 1940.

3. Johnston, J. A.: Factors Influencing Retention of Nitrogen and Calcium in Period of Growth: IV. Effect of Estrogen, Am. J. Dis. Child. **62**:708-715 (Oct.) 1941.

4. Johnston, J. A.: On the Possible Relation of Nutrition to the Development and Course of Tuberculosis, in Gardner, L. U.: Tuberculosis in Industry, New York, National Tuberculosis Association, 1942.

5. Leitch, I.: Determination of Calcium Requirements of Man, Nutrition Abstr. & Rev. **6**:553 (Jan.) 1937.

of the intake in grams calcium daily: from 6 months to 2 years 0.8 grams, from 2 to 9 years 0.9 grams, and from 9 years 1 gram increasing to 2 grams between 15 and 16 years," provide a generous allowance for the adolescent years and an extremely wide range. With an average American diet for this age group, deriving 15 per cent of the total calories from protein, 35 per cent from fat and 50 per cent from carbohydrate at a level of 2,400 calories with milk at each meal and an extra glass after school, a daily intake of 2 Gm. is seldom approached; and in the observations here cited retention was never greater than 40 per cent of the intake, after menarche it was considerably less. Leitch's recommendation for daily minimal intake at ages from 10 to 15 years is 1.37 Gm. Her method of arriving at these figures is criticized by McGowan [6] on statistical grounds, and indeed it would seem extremely difficult to plan an observation in this field that would be free from criticism, so many are the variables which affect retention and so ignorant are we of the desired goal; but if it is granted that retentions commensurate with good skeletal growth are to be sought, her approach has something to recommend it. The basic raw data, however, contain too many observations of a duration of questionable significance, and variations in amount of calcium ingested were seldom introduced. The recommended minimal intake, however, 1.37 Gm., does agree in general with the requirement based on the observations reported in this study.

More recently Duckworth and Warnock [7] offered a compilation of the balances listed in the literature, and their data for girls in the age group under discussion are as follows:

Age, Yr.	Intake, Mg.	Retention, Mg.
10 to 11	1,356	298
11 to 12	1,435	336
12 to 13	1,086	430
13 to 14	935	292

The relationship to vitamin D was not considered.

The value listed for girls 12 to 13 years old would be low except for those girls in whom menarche had been experienced and the demands of accelerated growth in length were no longer being made.

In compilations of data such as those made by Leitch and by Duckworth and Warnock care seems to have been exercised in the selection of data from some standpoints, for example the health of the patient, but little consideration seems accorded to what is probably the most important point, the duration of the uninterrupted observation. Any one conscious of the fluctuations in fecal calcium recognizes the truth of the statement by Porter-Levin [8] that a single statistically significant balance figure requires observation for fifteen to twenty days. In Duckworth's data, the standard for girls 13 years old was based on observation of a single patient for twenty-seven days and two other series of observations of five and eleven days' duration. Four series of observations on 12 year old girls were fifteen days or longer; these observations show a range of intake of calcium from 735 to 1,249 mg. with retention of 226 to 519 mg. My data [9] appear not to be included, presumably because it was assumed that the observations were made on abnormal children. The subjects used for the study of the effect of estrogen were normal girls who were in the Henry Ford Hospital because they were orphans; this hospital serves as a receiving home for such children until placement in suitable foster homes can be arranged. The ages of these girls ranged from 9 to 15 years, but all of them were physiologically close to the menarche. The subjects used for the study of the influence of puberty included 3 children who were normal to the extent that a clinician considers a child normal whose sole abnormality is a healed tuberculous first infection, something present in approximately 15 per cent of the entire population in this age group. Their stay in the hospital can likewise be considered as in lieu of residence in a home. Exercise, garden work and school sessions were part of their programs. The data obtained during the control periods in the study of the effect of estrogen are included in this summary.

CALCIUM

Relation of Intake to Retention.—Unlike reduced intakes of nitrogen, which will result in a positive balance ultimately, with a fall in the basal metabolism, there are intakes of calcium below which no retention occurs. Increased intakes are paralleled by increased retentions only up to a physiologic ceiling. Whether this maximum effective intake is also optimal is not known. There is much individual variation in the ability to retain calcium, influenced by a variety of factors, some of them hormonal, but chiefly by the state of the previous stores of this element. Because this last factor is so important studies of

6. McGowan, J. P.: Some Observations on Calcium Requirement Standards, Edinburgh M. J. **48**:484-500 (July) 1941.

7. Duckworth, J., and Warnock, G. M.: The Magnesium Requirements of Man in Relation to Calcium Requirements, with Observations on the Adequacy of Diets in Common Use, Nutrition Abstr. & Rev. **12**:167-183 (Oct.) 1942.

8. Porter-Levin, T.: Calcium and Phosphorus Metabolism of Normal Preschool Children: II. Successive Balance Studies Showing the Range of Variation in Calcium and Phosphorus Storage, J. Am. Dietet. A. **9**:22-35 (May) 1933.

9. Johnston (footnotes 3 and 4).

variables would seem more profitably made by intensive prolonged observation on a few subjects than by short term determinations of balance for many. The report on the influence of puberty is more significant because I had definite knowledge of the patients' intake of calcium for a year prior to the beginning of the observations, which then continued for two hundred and twenty-eight, one hundred and fifty and ninety-six days. With intake constant, information can be obtained on what can be stored in a given case, not on what might be stored with greater or smaller intakes.

If the intake of calcium is adequate and constant, utilization will vary with the rate of growth, and in particular this will be notable in the rapid acceleration preceding and the abrupt deceleration following menarche.

The retention of nitrogen may be unrelated to that of calcium and unaffected by variations in the intake of vitamin D. The synthesis of muscle tissue may proceed parallel with or bear a reciprocal relation to the formation of bone and we have no basis here for considering that there is any quantitative relation between the nitrogen balance and the intake of vitamin D. Determination of the nitrogen balance however, is essential in studies on utilization of calcium, since a negative nitrogen balance is known to produce a diminished retention of calcium.[10]

In all of my studies, a series of rotating diets was used the caloric level of which was dictated by the child's appetite. The composition of each was such that 15 per cent of the calories were derived from protein, 35 per cent from fat and 50 per cent from carbohydrate. The amount of calcium varied directly with the caloric intake, averaging 58.4 mg. per hundred calories of diet.

Source of Calcium in the Average Older Child's Diet.—The chief source of calcium in the diet of the average American child is milk. Sources other than milk in the 2,200 calory diet used in this study provided 328 to 466 mg. Analysis of milk continuously through the year showed a significant seasonal difference, the average calcium content in the winter months being 973 mg. per quart and in the spring and summer 1,331 mg. Accordingly, in studies made in the last eight years I have used a powdered preparation of milk, one lot of which would have a constant content of calcium for several months. When it is noted in some of the cases that a difference in intake of 0.2 mg. may mean the difference between a positive and a negative balance, the importance of a more exact knowledge of and provision for the optimal intake as well as the securing of its most efficient utilization by added vitamin D becomes evident.

The terms minimal and optimal are used here only in relation to retention, but whether or not the highest possible retentions are the most desirable is not known. In the metabolism of calcium there is definite evidence of the "physiologic ceiling" phenomenon noted with nitrogen; increased intake beyond a certain point results in no further retention. In the study of vitamin D, no attempt was made to explore the effects of massive doses, the range of daily doses investigated being from zero to 5,000 units.

The following study of a case bears on the matter of the relation of intake of calcium to retention. The subject was three years past menarche, and growth in height had apparently ceased.

CASE 1.—B. DeP., a girl, born Dec. 7, 1924, was observed to have a positive reaction to tuberculin at the age of 4 years (April 1929). Regular roentgen examinations showed nothing significant until April 1939, when a questionable patch of infiltration appeared in the upper lobe of the right lung. The child was admitted to the hospital for observation for tuberculosis of the reinfection type. The shadow persisted for several months but completely disappeared by August, so that for at least two months prior to the initiation of the studies of calcium balance there was no evidence of disease either roentgenographically or clinically, and there was no fever. Menarche occurred in November 1936. Between April and the beginning of the study, in October, the patient's weight increased from 104 pounds (47.2 Kg.) to 115 pounds (52.1 Kg.). The course of her changes in weight and height over the years preceding the observations is pertinent, her gain having been consistent until 1935, when, after a transfer from a good foster home to her own poor home, progress was interrupted; for a year she gained nearly 4 inches in height but actually lost ½ pound (0.5 Kg.) of weight. Between that time and the time of the detection of the suspicious lesion, however, the patient recovered weight and she seemed about average at the time of the study.

Date	Age, Yr.	Weight		Height, Inches
		Lb.	Kg.	
1/33	8	53	24	47
2/34	9	64	29	49.5
1/35	10	63.5	28.7	53.25
1/36	11	72	32.7	55.5
11/36	Menarche			
2/37	12	90	40.8	58
3/38	13.25	99.5	45.1	59.8
4/39	14.3	103	46.7	60
10/39 to 7/40	Study			
5/41	..	119	54	60

The observations on calcium balance covered two hundred and eighty-eight days (table 2 and chart 1), and the study was concerned with the amount of calcium to be added to a soybean preparation to promote retention of that element. Three variables were studied: caloric intake, source of calcium and amount of calcium. Two levels of caloric intake, 2,200 and 1,900 calories, were used; the higher intake produced gains in weight and a positive nitrogen balance; the lower intake produced loss of weight and a negative nitrogen balance. In the first period of eighteen days the calcium was derived largely from cow's milk; thereafter it was added to the soy-

10. Kunerth, B. L., and Pittman, M. S.: A Long Time Study of Nitrogen, Calcium and Phosphorus Metabolism on a Low Protein Diet, J. Nutrition **17**: 161-173 (Feb.) 1939.

TABLE 1.—*Calcium Balances of Nine Girls at Puberty*

Patient	Age, Yr.	Menarche*	Weight		Estimated Weight for Height and Age		Calcium Intake		Calcium Retention			Vitamin D, U. S. P. Units	No. of Days	Basal Metabolic Rate		Basal Calories	Comments
			Lb.	Kg.	Lb.	Kg.	Gm.	Gm./ Kg.	Gm.	Gm./ Kg.	% of Intake			Boothby	Wetzel		
F. G.	13	+⅛	117	53.1	106	48.1	1.488	0.028	0.570	0.011	38	0	18	−20	−9	1,241	
P. P.	13	+¼	98	44.5	82	37.2	1.374	0.030	0.503	0.011	37	0	18	+ 2	+9	1,395	
O. B.	15	+1	122	55.3	116	52.6	1.155	0.021	0.319	0.006	28	0	17	−16	−5	1,317	
J. S.	13⁹/₁₂	+1½	119	54.0	96	43.5	1.392	0.026	0.354	0.006	25	1,000	18	−10	−1	1,349	
N. M.	10⁷/₁₂	+⅓	110	49.9	100	45.4	1.298	0.026	0.316	0.006	24	0	18	−20	−3	1,296	
E. S.	9¼	....	70	31.8	74	33.6	1.125	0.035	0.315	0.009	28	..	15	− 9	−1	1,122	
V. G.	9⁸/₁₂	−⅓	80	36.3	68	30.8	1.216	0.034	0.495	0.014	40	0	77	− 7	±0	1,187	Before menarche
V. G.	9¼	+⅓	85	38.6	72	32.7	1.194	0.030	0.360	0.009	30	0	102	− 9	−1	1,201	After menarche
M. W.	10⅝	−⁵/₁₂	114	51.7	104	47.2	1.173	0.023	0.340	0.006	29	0	228	−17	−4	1,304	Before menarche
M. W.	11	+⅛	110	49.9	104	47.2	1.104	0.022	0.237	0.004	21	0	66	−23	−8	1,223	After menarche
D. W.	11½	−¹/₁₂	98	44.5	108	49.0	1.361	0.031	0.649	0.014	47	0	21	−11	+5	1,365	Before menarche
D. W.	11⁷/₁₂	+⅛	96	43.5	108	49.0	1.350	0.031	0.460	0.011	34	0	60	−14	+2	1,306	After menarche

* Years after (+) or years before (—) menarche.

TABLE 2.—*Data for B. deP.**

No. of Period (Each 18 Days)	Date	Nitrogen			Calcium					Basal Calories	Weight		Basal Metabolic Rate		Calories in Diet	Comments
		Output, Gm.	Intake, Gm.	Balance, Gm.	Urine, Gm.	Stool, Gm.	Total Output, Gm.	Intake, Gm.	Balance, Gm.		Lb.	Kg.	Boothby	Wetzel		
1	11/ 7 to 24	13.69	14.89	+1.20	0.152	1.146	1.298	1.478	+0.180	1,337	115	52.1	− 7	+2	2,200	
2	11/25 to 12/12	13.46	14.57	+1.11	0.129	0.683	0.812	0.825	+0.013	1,356	116	52.6	− 4	±0	2,200	Soybean milk plus dicalcium phosphate
3	12/13 to 30	13.39	14.80	+1.41	0.128	0.680	0.808	0.883	+0.075	1,376	116¾	52.9	− 4	+1		
4	12/31 to 1/17	13.39	14.49	+1.10	0.138	0.774	0.912	1.007	+0.095	1,292	117¼	53.2	−10	−5		
5	1/18 to 2/4	13.69	14.62	+0.93	0.130	0.928	1.058	1.169	+0.111	1,316	118½	53.8	− 8	−4		
6	2/ 5 to 2/22	14.27	15.08	+0.81	0.117	1.085	1.202	1.231	+0.029	1,349	117¾	53.3	− 6	−1		
	Averages	13.64	14.71	+1.07	0.128	0.830	0.958	1.023	+0.065	1,338						
7	2/23 to 3/11	14.52	15.18	+0.66	0.097	0.455	0.552	0.466	−0.086	1,344	119	54.0	− 7	−2	2,200	Soybean milk without dicalcium phosphate
8	3/12 to 29	12.55	11.75	−0.80	0.081	0.381	0.462	0.328	−0.134	1,265	118	53.5	−12	−7	1,900	
9	3/30 to 4/16	12.73	11.99	−0.74	0.101	0.785	0.886	0.791	−0.095	1,293	116¾	52.9	− 9	−5	.....	Dicalcium phosphate 0.466 mg.
10	4/17 to 5/4	12.36	12.22	−0.14	0.094	1.100	1.194	1.241	+0.047	1,278	116½	52.8	−11	−6	.....	Dicalcium phosphate 0.932 mg.
11	5/ 5 to 22	11.81	11.97	+0.16	0.074	1.647	1.721	1.641	−0.080	1,271	117	53.1	−10	−6	.....	Dicalcium phosphate 1.398 mg.
12	5/23 to 6/9	12.74	12.08	−0.66	0.090	1.803	1.893	2.115	+0.222	1,251	116¼	52.7	−12	−8	.....	Dicalcium phosphate 1.864 mg.
13	6/10 to 27	12.33	11.85	−0.48	0.114	2.024	2.138	2.542	+0.404	1,268	116	52.6	−12	−6	.....	Dicalcium phosphate 2.330 mg.
14	6/28 to 7/15	12.32	12.33	+0.01	0.107	2.796	2.903	3.005	+0.102	1,268	116	52.6	−12	−6	.....	Dicalcium phosphate 2.796 mg.
15	7/16 to 8.1	12.13	11.33	−0.80	0.101	2.989	3.090	3.446	+0.356	1,197	116	52.6	−10	−12	.....	Dicalcium phosphate 3.262 mg.

* Born Dec. 7, 1924; menarche Nov. 1936; height 59¾ inches.

bean preparation in the form of dicalcium phosphate. While the patient was receiving the higher caloric intake with the preparation of soybean and dicalcium

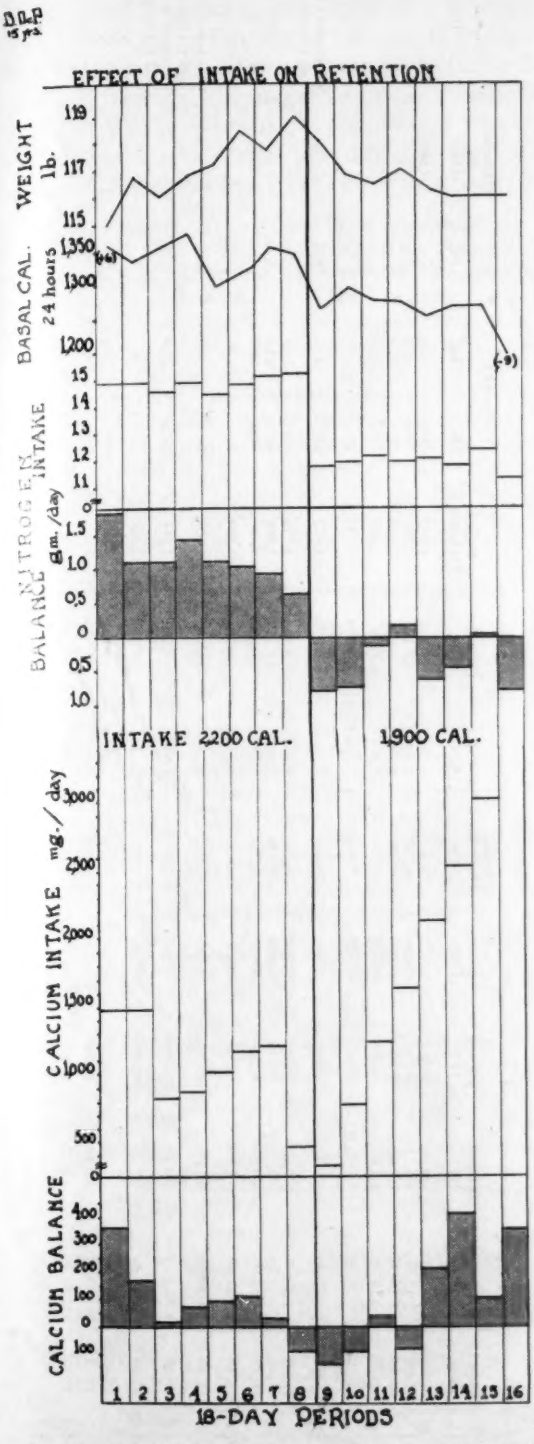

Chart 1 (B. deP.).—During the first period of eighteen days the calcium was derived largely from cow's milk; thereafter it was added to the soybean preparation in the form of dicalcium phosphate.

phosphate, daily intakes of calcium ranged from 466 to 1,231 mg. On all levels of calcium intake except the lowest positive balances prevailed. The highest retention occurred with an intake of 1,169 mg. The greater output which occurred in the following period, when the intake was 1,231 mg., may represent a "spill" of transiently held calcium. With the lower caloric level the intake of calcium ranged from 328 to 3,446 mg. per day and the balances from minus 134 to plus 404 mg. per day. With this highest level of retention (404 mg.), the "physiologic ceiling" seemed to have been reached and passed, for in the next period, with even higher intake, retention fell to 102 mg. per day. No added source of vitamin D was used. The effect of a negative nitrogen balance in rendering insufficient an otherwise adequate intake of calcium is described by Kunerth and Pittman.[10]

While exactly equivalent amounts of calcium were not given in the diets of cow's milk and of soybean with added dicalcium phosphate, comparable retention occurred; 12 per cent of a daily intake of 1,478 mg. was retained when the calcium was derived chiefly from cow's milk and 10 per cent of a daily intake of 1,169 mg. when it was derived from dicalcium phosphate in the soybean preparation. Considering only the observations made while the diet consisted of soybean with added calcium, during the period of positive nitrogen balance and gain in weight there was a steady increase in retention paralleling the increases in daily intake of calcium from 825 to 1,169 mg.; beyond this limit retention diminished. In the period when weight was being lost and the nitrogen balance was negative, twice as great an intake of calcium was required to produce retention of calcium and the ceiling was not reached until about 2,500 mg. were taken daily. Part of this increase in the requirement may be referable to the fall in the basal metabolic rate.

VITAMIN D

The function of vitamin D in the older child would superficially seem to be no different from that which has been shown for the infant. Its stabilizing effect has been noted, but an actual need for the vitamin seems questioned. No supplementary vitamin D was given the 9 children for whom data are listed in table 1. Its use will reduce the negative calcium balance noted with an inadequate intake of calcium, but unless the latter is marginal vitamin D will not promote a positive balance. Yet the acceleration of growth in height which precedes puberty would seem to make the desirability of supplementary vitamin D in this period comparable to that in infancy. The increased activity and greater exposure to light of older children compared with infants should quantitatively influence the requirement; but aside from the suggestion of Jeans and Stearns [1b] that larger amounts were less effective than smaller and the repeated demonstration of the toxicity of extremely large doses, there is little information comparing the effects of various levels of vitamin D intake. A few studies are included on this point. The source of vitamin D used in these observations was an especially assayed viosterol in oil furnished by Mead Johnson and Company, one drop of which contained 200 U. S. P. units of vitamin D.

TABLE 3.—*Data for A. S.*

No. of Period (Each 15 Days)	Date	Nitrogen			Calcium					Total Calories	Weight		Height, In.	Calories in Diet	Comments
		Output, Gm.	Intake, Gm.	Balance, Gm.	Urine, Gm.	Stool, Gm.	Total Output, Gm.	Intake, Gm.	Balance, Gm.		Lb.	Kg.			
1	9/6 to 22	10.08	11.91	+1.83	0.185	1.031	1.216	1.071	−0.145	1,258	119	54	58¼	1,900	
2	9/23 to 10/10	10.59	11.63	+1.04	0.154	1.153	1.307	1.114	−0.192	1,162					
	Averages	10.34	11.77	+1.43	0.169	1.092	1.261	1.093	−0.168	1,210					
3	10/11 to 28	10.82	12.66	+1.84	0.092	1.118	1.210	1.140	−0.070	1,260	...	..	....	.....	1,950 U. S. P. units vitamin D
4	10/29 to 11/15	10.52	12.05	+1.53	0.042	0.988	1.030	1.343	+0.313	1,262	...	..	....	.....	1,950 U. S. P. units vitamin D and dicalcium phosphate 233 Gm.
5	11/16 to 12/3	11.20	12.15	+0.95	0.023	1.262	1.285	1.578	+0.293	1,270	108	49	59¼	.....	1,950 U. S. P. units vitamin D and dicalcium phosphate 466 Gm.
6	12/4 to 21	11.14	12.64	+1.50	0.014	1.192	1.206	1.556	+0.350	1,219	...	..	....	.....	650 U. S. P. units vitamin D and dicalcium phosphate 466 Gm.

TABLE 4.—*Data for E. S.*

No. of Period (Each 18 Days)	Date	Nitrogen			Calcium					Total Calories	Weight		Height, In.	Calories in Diet	Comments
		Output, Gm.	Intake, Gm.	Balance, Gm.	Urine, Gm.	Stool, Gm.	Total Output, Gm.	Intake, Gm.	Balance, Gm.		Lb.	Kg.			
1	12/13 to 29	11.49	11.97	+0.50	0.015	0.871	1.097	1.103	+0.217	1,125	69½	31.5	55	1,900	
2	12/30 to 1/16	11.00	12.21	+1.21	0.012	0.839	0.851	1.110	+0.259	1,122	70½	32.0	55¼	.....	
3	1/17/ to 2/3	10.84	12.00	+1.16	0.028	0.781	0.809	1.125	+0.216	1,098	71	32.2	....	.....	
4	2/25 to 3/14	11.11	12.38	+1.27	0.023	0.798	0.821	1.123	+0.302	1,124	73¾	33.5	....	.....	
	Averages	11.11	12.14	+1.03	0.019	0.822	0.841	1.115	+0.274	1,117					
5	3/15 to 4/1	11.05	12.58	+1.53	0.009	0.749	0.758	1.035	+0.325	1,075	73	33.1	56¼	.....	Viosterol (1,500 U. S. P. units of vitamin D)
6	4/2 to 19	11.50	12.22	+0.72	0.010	0.780	0.790	1.083	+0.293	1,118	73	33.1	....	.....	
7	4/20 to 5/7	11.33	12.16	+0.83	0.010	0.810	0.820	1.090	+0.270	1,090	73	33.1	....	.....	
8	5/8 to 25	11.22	12.07	+0.85	0.007	0.832	0.839	1.160	+0.321	1,113	73¼	33.2	....	.....	
	Averages	11.35	12.15	+0.80	0.009	0.807	0.816	1.111	+0.295	1,107					
9	5/26 to 6/12	11.03	12.39	+1.36	0.010	0.773	0.783	1.150	+0.367	1,075	73	33.1	56½	.....	Viosterol (3,000 U. S. P. units of vitamin D)
10	6/13 to 30	11.57	12.32	+0.75	0.009	0.695	0.704	1.087	+0.383	1,017	72½	32.9	....	.....	Viosterol (3,000 U. S. P. units of vitamin D)
	Averages	11.30	12.35	+1.05	0.009	0.734	0.743	1.118	+0.375	1,046					
11	7/1 to 7/18	11.74	12.37	+0.63	0.006	0.788	0.794	1.080	+0.286	1,065	72	32.7	57	.....	
12	7/19 to 8/5	11.52	12.44	+0.92	0.018	0.843	0.861	1.082	+0.221	1,002	72½	32.9	....	.....	
	Averages	11.63	12.40	+0.77	0.011	0.815	0.826	1.080	+0.254	1,033					

In the study reviewed in the following report on a case there are two variables, the intake of calcium and the intake of vitamin D. With the intake of calcium practically constant the ingestion of 1,950 U. S. P. units of vitamin D as viosterol daily for a period of eighteen days (table 3, period 3) reduced the negative calcium balance from 168 to 70. The urinary excretion of calcium dropped to 77 mg. per day but this decrease did not promote a positive calcium balance.

CASE 2.—*History.*—A. S., a girl, born prematurely and weighing 1,532 Gm. at birth, was fed at the breast and received cod liver oil during the first year. Her second winter was spent in Florida. When she was 5 years old a scoliosis was noted, which steadily progressed, and when she was 10 a Hibbs fusion operation was done, and she was confined in a body cast. It was after this operation that the metabolic observations were made. The child's diet during the year preceding this study had included a quart of milk a day but no added source of vitamin D. During the first period of these studies (September 6 to September 22) the patient was at rest in bed; during the remainder of the period of observation she was walking about the ward.

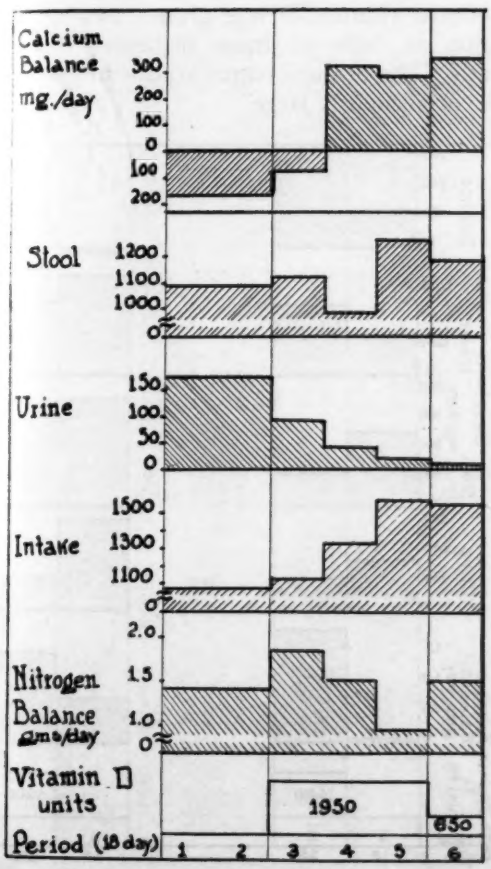

Chart 2 (A. S.).—No retention of calcium occurred until the intake reached 1,343 mg. per day, though the range between 1,140 mg. and this figure was not explored. Ingestion of vitamin D reduced the extent of the negative balance with a calcium intake of 1,140 mg. but did not make it positive. Increases in the intake of calcium beyond 1,343 mg. resulted in no significant increase in retention.

Study of Calcium Balance.—The study of the nitrogen and calcium balances covered one hundred and eight consecutive days, during which time there were three levels of calcium intake and two levels of vitamin D intake.

With a daily intake of approximately 1,100 mg. of calcium the metabolic balance for this element was negative; the negative balance was reduced but not made positive by the administration of 1,950 U. S. P. units of

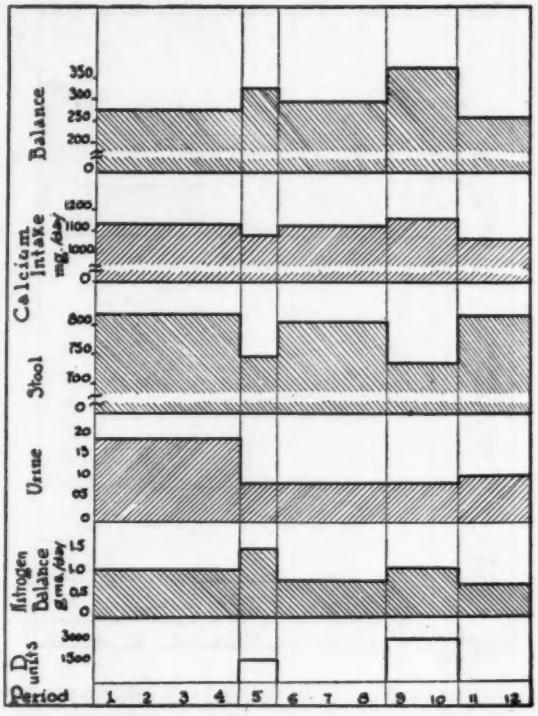

Chart 3 (E. S.).—With the intake of calcium constant at approximately 1,100 mg. per day, retention increased with added vitamin D; 3,000 U. S. P. units of vitamin D was more effective than 1,500. Both fecal and urinary losses diminished with the ingestion of additional amounts of the vitamin.

vitamin D. On a daily intake of 1,343 mg. of calcium the patient stored 313 mg. daily. The storage was not increased by the addition of dicalcium phosphate to bring the intake up to 1,578 mg. In the final period of observation the intake of vitamin D was reduced to 650 U. S. P. units daily and the highest retentions of calcium were noted. Since this period was continuous with two previous ones during which the patient received 1,950 U. S. P. units daily, the effect of which would still be present to a degree, comparisons of differences in the level of vitamin D are not possible here. The observation brings out the following facts: (1) that vitamin D does not affect the storage of calcium, though with it urinary loss is diminished when the intake of calcium is below a minimal level; (2) that in this girl the minimal level was approximately 1,300 mg. and (3) that there is probably a physiologic ceiling beyond which retention of calcium does not increase with increasing intake, which in this case was 1,300 mg., or 26 mg. per kilogram of body weight, per day.

Nitrogen retention increased transiently following the administration of vitamin D. The basal metabolic rate was minus 8 (Wetzel).

CASE 3.—E. S., a child 8 years old, was hospitalized for the treatment of phlyctenular conjunctivitis. She

reacted to tuberculin and showed a healed first infection in the lung. She is included here rather than with the patients with tuberculosis because it is felt that her condition was local and unaccompanied by systemic disturbance. Her history showed an apparently adequate diet, though she had had no cod liver oil for several years.

The patient was readmitted to the hospital because of an exacerbation of the conjunctivitis at the age of

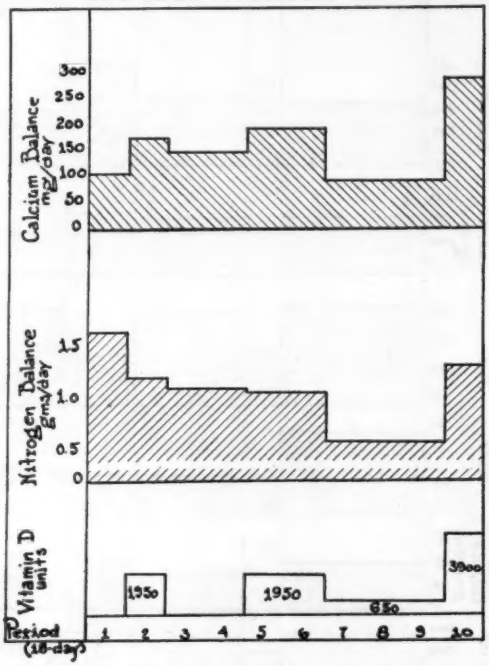

Chart 4 (H. S.).—With the intake of calcium constant at approximately 1,100 mg. per day, increasing retentions of calcium paralleled increasing intakes of vitamin D in amounts from zero to 3,900 U. S. P. units.

10 years. No secondary sexual characteristics had yet appeared. She was afebrile throughout the period of observation and was active around the ward, but she was receiving minute desensitizing doses of tuberculin.

Nitrogen and calcium balances were determined uninterruptedly from Dec. 13, 1940 to Aug. 5, 1941. The intake of both calcium and nitrogen was practically constant throughout the observations which covered three periods during which she received no vitamin D, one in which she received 1,500 U. S. P. units daily and another in which she received 3,000 U. S. P. units daily.

The patient at all times had a positive calcium balance, but the peak retention occurred while she was receiving 3,000 U. S. P. units of vitamin D daily. The increased retention is referable to a diminution in both fecal and urinary losses. Nitrogen retention showed a significant increase also during each period in which viosterol was administered. The basal metabolic rate was not significantly changed.

CASE 4.—*History.*—H. S., a girl, was born in September 1926. Menarche occurred in March 1938, when she was 12 years old. The patient was hospitalized with tuberculous pleural effusion in January 1941 and became afebrile in May. Observations on calcium retention were begun in August 1941, and between May and August her weight had increased from 118 to 140 pounds (53.5 to 63.5 Kg.) on a "free" hospital diet containing more than 1 Gm. of calcium daily but not accurately measured. Her data are included here rather than with the reports on patients with tuberculosis since she had shown no evidence of illness for three months; she had presumably effected a replenishment of stores during that time, gaining 22 pounds (10 Kg.) on a diet containing a liberal amount of calcium.

Study of Calcium Balance.—Uninterrupted observations were made for one hundred and eighty days on this 15 year old girl who was three and a half years past the menarche and no longer growing in height. The intake of calcium was approximately constant at 1,100 mg. daily. During three periods of eighteen days each she received no supplementary vitamin D; during seven periods she received amounts varying from 650 to 3,900 U. S. P. units daily. Retention of calcium roughly paralleled these levels and was highest with the highest intake of the vitamin.

Two patients with slipped upper femoral epiphysis showed an abnormality of calcium retention which was improved with administration of vitamin D. In one patient (P. A.) a slightly negative balance became positive. The other patient (D. M.) showed a much lower initial calcium retention than would be expected for this age, and retention was doubled when additional vitamin D was given. Nitrogen retention in both of these instances increased greatly. The urinary output of calcium of P. A. was conspicuously large.

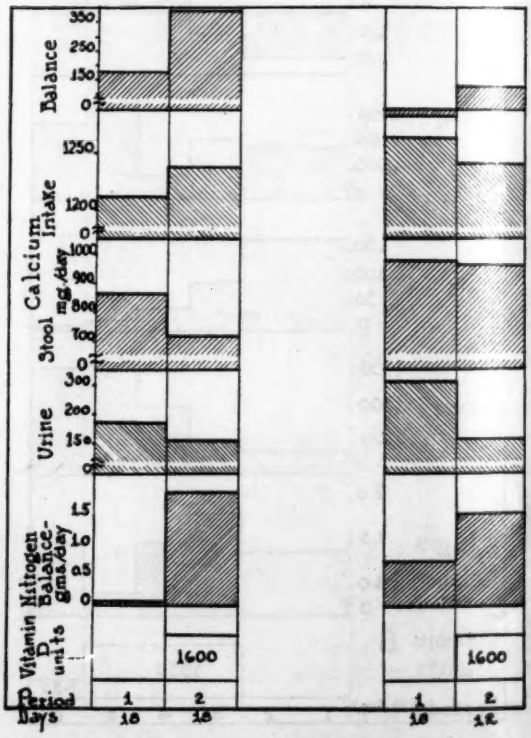

Chart 5 (D. M. and P. A.).—On daily intakes of calcium averaging 1,237 mg., the administration of 1,600 U. S. P. units of vitamin D resulted in the conversion of a negative calcium balance to a positive balance in one patient and the doubling of a low positive balance in the other. Both patients had epiphysiolysis of the upper end of the femur. The high urinary loss of calcium is notable in one (P. A.).

TABLE 5.—*Data for H. S.*

No. of Period (Each 18 Days)	Date	Nitrogen			Calcium					Total Calories	Weight		Height, In.	Calories in Diet	Comments
		Output, Gm.	Intake, Gm.	Balance, Gm.	Urine, Gm.	Stool, Gm.	Total Output, Gm.	Intake, Gm.	Balance, Gm.		Lb.	Kg.			
1	8/22 to 9/7	10.47	12.16	+1.69	0.102	0.902	1.004	1.108	+0.104	1,434	141.5	64.2	64¾	1,900	
2	9/8 to 25	10.90	12.14	+1.24	0.089	0.833	0.922	1.098	+0.176	1,507	140	63.5	....	.....	1,950 U. S. P. units vitamin D
3	9/26 to 10/13	10.93	12.01	+1.08	0.084	0.878	0.962	1.136	+0.174	1,421	138.5	62.8	....	.....	Vitamin D discontinued
4	10/14 to 31	11.25	12.44	+1.19	0.084	0.916	1.000	1.132	+0.132	1,390	137.5	62.3	....	.....	
	Averages	11.09	12.22	+1.13	0.084	0.807	0.981	1.134	+0.153	1,405					
5	11/1 to 18	11.16	12.46	+1.30	0.095	0.792	0.887	1.133	+0.246	1,369	135	61.2	....	.....	1,950 U. S. P. units vitamin D
6	11/19 to 12/6	11.31	12.22	+0.91	0.087	0.875	0.962	1.108	+0.146	1,393	134	60.8	....	.....	
	Averages	11.24	12.34	+1.10	0.091	0.833	0.924	1.120	+0.196	1,381					
7	12/7 to 24	11.56	12.60	+1.04	0.085	0.976	1.061	1.090	+0.029	1,366	132	59.9	....	.....	650 U. S. P. units vitamin D
8	12/28 to 1/13	12.24	12.30	+0.06	0.078	0.876	0.954	1.108	+0.154	1,322	132	59.9	....	.....	
9	1/14 to 31	11.44	12.22	+0.78	0.070	0.921	0.991	1.094	+0.103	1,348	131	59.4	....	.....	
	Averages	11.75	12.37	+0.62	0.078	0.924	1.002	1.097	+0.095	1,345					
10	2/1 to 18	11.22	12.54	+1.32	0.055	0.775	0.830	1.122	+0.292	1,297	...	....	....	.....	3,900 U. S. P. units vitamin D

TABLE 6.—*Data for D. M. and P. A.**

D. M.		Dates	Nitrogen			Calcium					Total Calories	Weight		Height, In.	Calories in Diet	Comments
			Output, Gm.	Intake, Gm.	Balance, Gm.	Urine, Gm.	Stool, Gm.	Total Output, Gm.	Intake, Gm.	Balance, Gm.		Lb.	Kg.			
18 day period	No. 1	7/1 to 17	13.78	13.82	+0.04	0.184	0.851	1.035	1.210	+0.175	1,350	104	47.2	61¾	2,200	
18 day period	No. 2	7/18 to 8/4	12.25	14.15	+1.90	0.153	0.711	0.864	1.232	+0.368	1,407	105	47.6	61¾	.....	Viosterol in oil, 8 drops, 1,600 U. S. P. units
P. A.																
18 day period	No. 1	11/15 to 12/2	11.98	12.74	+0.76	0.318	0.987	1.305	1.266	−0.039	1,317	87	39.5	60½	1,900	
12 day period	No. 2	12/3 to 14	10.91	12.46	+1.55	0.159	0.960	1.119	1.240	+0.121	1,324	86½	39.3	....	.....	Viosterol in oil, 8 drops, 1,600 U. S. P. units

* Observations on D. M. began three days and on P. A. seven days after ether anesthesia.

CASE 5.—D. M., a girl born in July 1927, was first seen at 8 months of age, with bronchopneumonia and mild rickets. She had a history of adequate feeding save for the omission of any added source of vitamin D. She weighed 19 pounds (8.6 Kg.) at this time. At 3 years of age she had a tonsillectomy and adenoidectomy because of frequent infections. Her progress in height and weight from then on was as follows:

Date	Age, Yr.	Weight		Height, Inches
		Lb.	Kg.	
11/30	3½	33	15	39
9/35	8	55	24.9	49½
5/38	11	73	33.1	55½
6/39	12	91	41.3	59
7/40	13	104	47.2	61¾

A limp developed during the summer of 1938, and in October of that year there was roentgenographic evidence of a slipped upper femoral epiphysis on the left. The epiphysis was nailed. Preoperatively it was possible to determine the calcium balance for four days. This period was not of sufficient length to be significant, but in the light of the data from later observations over a longer period the results are interesting, particularly because of the high urinary output. The daily intake of calcium was 1,518 mg., and the output was 1,582 mg. in the stool and 392 mg. in the urine, giving a balance of minus 0.457 mg. The nitrogen balance was minus 0.57 mg. per day.

In July and August 1940 continuous observation for thirty-five days showed in the first period of eighteen days a retention of 175 mg. a day with an intake of 1,210 mg. of calcium; the retention increased to 368 mg. a day with the administration of 1,600 U. S. P. units of vitamin D as viosterol. The nitrogen balance also increased significantly. This balance is representative of the year following the period of sharp increase in the rate of growth preceding menarche, and it cannot be considered characteristic of the situation at the time the femoral epiphysis slipped. She had, in the year preceding this balance been on an adequate intake of vitamin D and calcium, started when the condition was recognized.

While the earliest balance cannot be considered conclusive because of the shortness of the period of observation, the urinary output, a factor which is trustworthy in shorter periods, was unusually high and corresponded to that observed in a similar case here reported (P. A.).

CASE 6.—P. A., a girl born in May 1927, was found to have a slipped upper epiphysis of the left femur in November 1938. Her symptoms dated from a fall which she had had four months previous to that time. The epiphysis was nailed in place. One year later, when the child was 12½ years old, the same condition appeared in the right hip. Our observations on the calcium and nitrogen balances were made a year later, during her stay in the hospital for the removal of both nails. During the two years which preceded the observations she had an average diet which included three glasses of milk and 500 U. S. P. units of vitamin D daily, with adequate meat, vegetables, fruit and eggs.

Study of the intake and output of calcium for thirty days showed a negative balance of 39 mg. per day for a control period of eighteen days on a daily intake of 1,266 mg. of calcium and a positive balance of 121 mg. per day during the remaining twelve days on an intake of 1,240 mg. per day (there had been some refusal) with 1,600 U. S. P. units of vitamin D. This is not descriptive of the condition at the time the epiphysis slipped, but, as in the case previously described, the retention of nitrogen was doubled when vitamin D was administered.

SUMMARY

An average daily intake of 1,286 mg. of calcium (range 1,100 to 1,500) resulted in an average retention of 410 mg. (range 237 to 649), or an intake of 28 mg. per kilogram of body weight (range 21 to 35) resulted in a retention of 9 mg. per kilogram of body weight (range 4 to 14) without ingestion of supplementary vitamin D. Vitamin D (as viosterol) increased the retention of calcium and the increase paralleled the amount of vitamin D ingested up to 3,900 U. S. P. units. In 1 patient, a girl who had a slipped femoral epiphysis, the ingestion of supplementary vitamin D resulted in changing a negative to a positive balance when the intake of calcium was 1,250 mg. per day. In a second instance of the same condition, a small balance (175 mg.) was more than doubled (368 mg.) by the administration of 1,950 U. S. P. units of vitamin D daily.

The amounts of vitamin D given to these older children when considered in terms of units of the vitamin per unit of body weight are comparable to the smaller amounts used for infants though there is no definite proof beyond these increased retentions that the requirement for this vitamin is related to body size. It seems more likely that the amount required may be related to the variations in the speed of increase in body length; the requirement would therefore be increased during the period of accelerated growth in height preceding sexual maturation.

There is a threshold a little below the average intake, below which no retention occurs, and there is a physiologic ceiling beyond which increased intake does not promote further retention. The margin of safety to insure storage in girls at puberty is small, and the data obtained from this study confirm the need for a full quart of milk per day in the diet during the pubertal period. A liberal intake of vitamin D at this period is desirable. The administration of amounts varying from 650 to 3,900 U. S. P. units of vitamin D in the form of a concentrate was paralleled by increases in the amounts of calcium retained; within this range no evidence of a depressing effect with the higher doses was noted.

Dr. Frank Hartman supervised the determinations of basal metabolic rate; Dr. O. H. Gaebler supervised the determinations of calcium and nitrogen balance. Dr. Philip Jeans and Dr. Genevieve Stearns reviewed and criticized the manuscript. The assayed preparation of viosterol was provided by the Mead Johnson Company.

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OCCLUSION OF URETHRAL MEATUS

MAURICE MUSCHAT, M.D.
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Occlusion of the urethral meatus is variously called "pinpoint meatus," "meatitis," "diaper ulcer," "acid burn" or "urine sore." Each term designates a particular stage of the same disease and attempts to indicate its etiologic factor.

The pathologic condition under discussion is seen in a great number of boys during the first year of life but may become apparent only after the second or third year.

CLINICAL PICTURE

The clinical picture (fig. 1) begins with redness of the urinary meatus, followed by slight

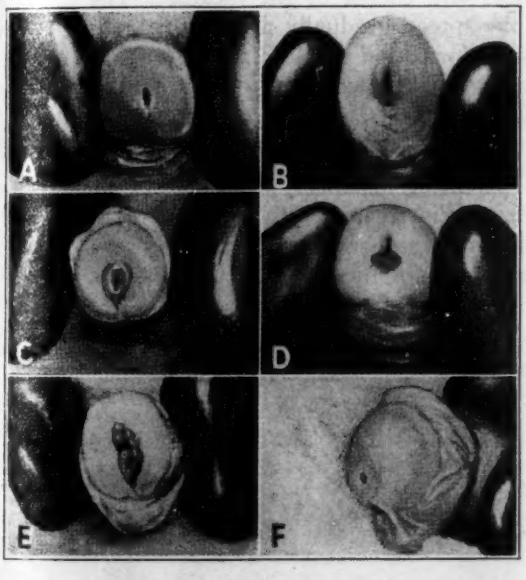

Fig. 1.—Photographs showing the various stages of the disease of the meatus; (*A*) beginning inflammation, (*B*) acute edema, (*C*) chronic inflammation with discharge, (*D*) ulceration, (*E*) cicatrization and healing and (*F*) final healing with pinpoint meatus. (Reproduced from article by H. P. Winsbury-White, *Brit. J. Urol.* **13**:149, 1941.)

edema of the urethral lips with a seropurulent discharge and occasional bleeding. As the condition progresses the acute inflammation subsides, turning into a chronic inflammation with a discharge and with gluing together of the lips. Minute ulcers appear on the inner side of the mucosa, gradually extending outward and involving the skin. At this stage the formation of crusts occurs. Urination becomes painful. The scab is torn off at each voiding, with oozing of blood from the raw surface. During this stage a healing process is progressing below the crusts. The minute ulcers are healing with the formation of scars, thus gradually reducing the size of the urethral meatus to a pinpoint. Voiding becomes difficult and painful. Reduction in size and force of the urinary stream is noted, and permanent, incomplete occlusion ensues. The occlusion is equivalent to a urethral stricture and, clinically, produces identical though less severe symptoms.

In many such instances the occlusion remains incomplete, and after healing has ensued no further constriction occurs. While the urinary stream is greatly reduced in size, it has enough force, due to compensatory muscular hypertrophy of the bladder, to insure complete emptying of the bladder. Patients with this condition exhibit no apparent ill effect later. On careful study, however, one can find notable hypertrophy of the musculature of the bladder. The urinary apparatus works like a properly compensated, adjusted and balanced mechanism, without the patient's being aware of any difficulty. The cystic hypertrophy in these patients is comparable to the ventricular hypertrophy of the heart after an attack of valvulitis with the resulting formation of scars and valvular constriction. The patient is unaware of the cardiac condition until it is discovered by auscultation and percussion, just as the hypertrophy of the bladder is found only on cystoscopy.

Such is the complete clinical picture of occlusion of the urethral meatus, from its insignificant beginning to the most serious, permanent results. But this complete picture is not seen in all cases; the condition may regress long before ulceration has occurred. Frequently the acute inflammation subsides, leaving only a mild, chronic condition, with a serous discharge or none at all.

The preponderance of the fortunate outcome just described is responsible for the slight interest in this condition shown by pediatricians. Only in a small number of cases does the disease become chronic, with the ultimate major

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effects. Their number, however, is large enough to justify careful study and to demand properly controlled management.

CAUSATION

There is no accepted cause for this condition. Wet diapers and ammoniacal, scalding urine are

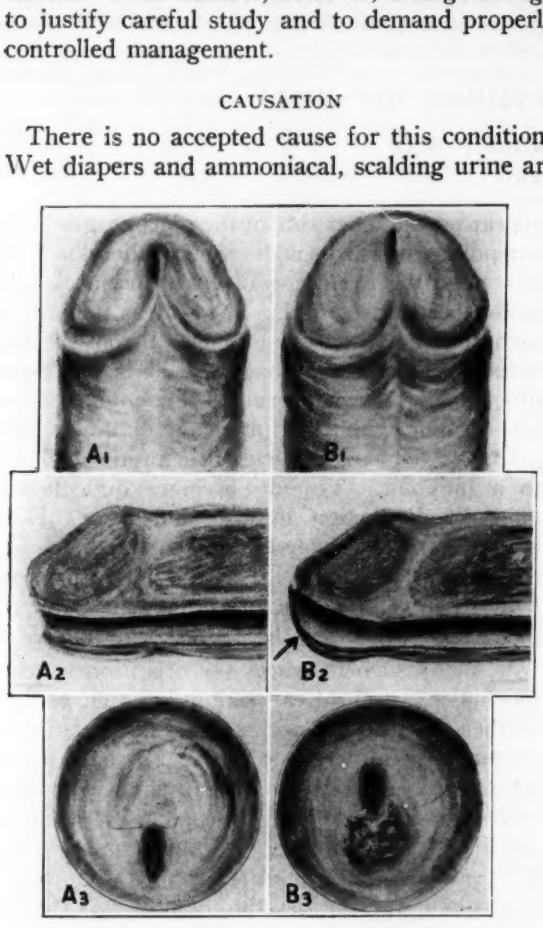

Fig. 2.—Drawings illustrating the urethral structure in a normal infant (*A*) and in an infant with malposition of the urethral meatus (*B*). Part 1 compares the external appearances. Note the high position of the meatus in *B* as compared with the normal. Part 2 shows cross sections to illustrate the "dam" formation in the fossa navicularis (arrow) in *B*. Part 3 shows the fossa navicularis from within showing the ulcerations produced by continuous pounding of the urinary stream against the existing dam.

mainly held responsible for its development. While studying cases of urethral occlusion over a period of years, it became apparent to me that chemical changes in the urine alone cannot be held responsible for it. One sees many patients with cystitis with badly infected, alkaline urine without meatitis and, on the other hand, many with inflammation of the meatus with absolutely normal urine. The ulceration appears to originate inside the urethra, in the fossa navicularis, and not outside, throwing doubt on the postulated theory of external (diaper) origin of the disease.

There is one characteristic feature in these cases which has not been noted before. Observing the position of the meatus in patients with this disease, I found that it was much higher than in normal infants (fig. 2). The distance between the lower end of the meatus and the frenulum is much greater. The tissue in this area is thick and firm and is frequently hardened by coexisting scar tissue on its inner surface. This can readily be demonstrated by inserting a small, straight metal instrument and holding it tight against the inner surface of the canal.

I believe that the real reason that the inflammatory condition occurs in only a small number of babies is that it does occur only in infants in whom the urethral meatus is congenitally misplaced. When one visualizes the frontal end of the urethral canal in such infants, one is confronted with the existence of a wall or "dam" toward which the urine must flow. There must be a forceful impact of the powerful stream of urine against this dam at every urination. Such continuous pounding may cause alterations in the epithelium of the mucosa, with a breakdown of the surface and finally the formation of ulcers. Such ulcers become infected easily, causing redness and edema of the meatus. The infection may spread gradually to the surrounding tissues with formation of ulcers, scabs and, later, scars, until finally occlusion occurs and a pinpoint meatus results.

TREATMENT

In most instances ulceration of the urethral meatus is treated with ointments. If the condition is stubborn the patient is referred to a urologist for meatotomy. This is an office pro-

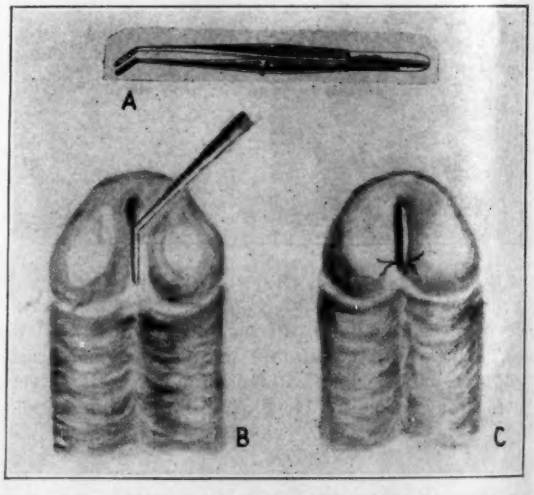

Fig. 3.—Drawings illustrating the operative procedure in removing the "dam"; *A*, ophthalmic advancement forceps; *B*, position of the forceps before removal of the dam, and *C*, the large urethral meatus after removal of the dam, with the one or two catgut sutures inserted with an atraumatic needle.

cedure and is easily accomplished. The mother is instructed to pull the cut lips apart several times a day. In many instances this treatment

is all that is necessary. The increased size of the meatus allows for better drainage, and the urethral inflammation disappears. Often this procedure is inadequate, because of rapid healing over of the cut surfaces. Bougies are then recommended to keep the meatus open, and daily treatments, continued over a long period, become necessary.

Recognizing this condition as the result of a congenital misplacement of the opening of the urinary canal, I have adopted a more direct approach to its cure. With the infant under light ether anesthesia, the excess wall is grasped with ophthalmic advancement forceps (fig. 3) in the midline, and, by sharp dissection along the blades of the forceps, an oblong piece of tissue about 1 by 5 mm. is removed. With an atraumatic needle, one or two catgut sutures are placed on each side of the bottom of the cut, not only for hemostasis but to prevent primary union of the cut surfaces (fig. 3). There is never any need for further treatment, and no dilatations are required, as the opening remains permanently large.

While this suggested procedure, requiring hospitalization for several hours, may appear as a more major undertaking than a rapid meatotomy performed in the office, it seems to me to be much more worth while. It not only represents a single procedure with a permanent cure but eliminates the countless shocks of frequent instrumental dilations.

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DENTAL CARIES AS INFLUENCED BY FAT VERSUS CARBOHYDRATE IN THE DIET

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Several articles published recently from this institution have dealt with the caries experience of diabetic children who were observed intermittently for long periods.[1] Evidence has been offered to indicate the lessening of the progression of caries in these children through dietary means. The protective effect has been attributed to the completeness of the diet, without attempt to indicate the part which might be played by any single characteristic of the diet.

During the course of the reported studies a sharp break in dietetic policy was made, even though the nutritional characteristics of the diets were not changed notably either from a qualitative or from a quantitative standpoint. This change consisted of the replacement of the original high fat diets by diets which offered only half as much fat and twice the amount of carbohydrate. The study herein recorded was designed to determine whether such a change in diet was associated with any tendency toward progression or further retardation of dental caries.

In both periods of the study the type diets contained fixed proportions of protein, carbohydrate and fat. Multiples of a fixed dietary unit were used in amounts determined by the physical needs of each child. The dietetic formula for each child provided 1 Gm. or more of protein for each pound (0.5 Kg.) of theoretic weight as determined from his height; it also provided caloric equivalence for full activity, a luxus of all recognized protective factors and a predetermined ratio of fatty acid to dextrose. During the first three or four years of the study the ratio of protein, carbohydrate and fat in the fixed diet was 7:9:21. When it had been demonstrated that the amount of insulin required was determined by the total calories rather than by the potential dextrose content of the diet (unpublished data), the use of high fat, low carbohydrate diets was abandoned. Thereafter diets with an intermediate content of fat and carbohydrate were employed. By 1933 the diets of most of the patients had been changed to provide a fatty acid: dextrose ratio ranging from 1:1.5 to 1:2, and the patients coming under the care of the diabetic service thereafter received such diets routinely. The caloric allowance of the high fat diets had proved greater than was needed for the maintenance of desirable weight; therefore the diets which were lower in fat also were decreased in caloric equivalence by about 25 per cent.

PRESENTATION OF DATA

The recorded observations relate to the dental courses of 59 girls and 52 boys who were observed recurrently for not less than three years each during the routine management of diabetes.

For a discussion of the regimen employed and a detailed review of the course of each child the reader is referred to an earlier report of this series.[1c]

For the purpose of this study the dental records previously reported have been partitioned in accordance with the fatty acid: dextrose ratio of the diet prescribed for the corresponding period. Diets with fatty acid: dextrose ratios from 1½:1 to 1:1 have been considered jointly under the designation "high fat"; those with ratios ranging from 1:1½ to 1:2 have been grouped as a unit under the designation "lower fat." Periods of observation of less than eighteen months have been omitted from statistical consideration so that errors inherent in the possible latency of caries would be ruled out. Forty-six children were observed for the minimum period or longer with each of the two levels of ingestion of fat; in each instance the high fat regimen preceded the one which provided a lower intake of fat. Twenty-six subjects were similarly observed solely while receiving the high fat diet, and 39 were observed solely while receiving the diet lower in fats.

Table 1 provides a summary of the dental responses of the subjects and permits comparison of the responses under the contrasted levels of

From the Department of Pediatrics, College of Medicine, and the Department of Pedodontics, College of Dentistry, State University of Iowa.

1. Boyd, J. D.: (*a*) Prevention of Dental Caries in Late Childhood and Adolescence, J. Am. Dent. A. **30**: 670 (May) 1943; (*b*) Dietary Control of Enamel Caries, ibid. **30**:1344 (Sept.) 1943; (*c*) Long Term Prevention of Tooth Decay Among Diabetic Children, Am. J. Dis. Child. **38**:721 (Oct.) 1943.

fat intake. In this table the periods of study are partitioned not only on the basis of the level of ingestion of fat but on the previous or subsequent dietary pattern. Thus there are separate compilations relating to the children observed for a significant interval (eighteen months or longer) solely under the high fat regimen, solely under the lower fat regimen, with an initial high fat diet (to be followed later by lower intake of fat) and with the subsequent lower level of ingestion of fat. The table includes the number of subjects studied under each specified condition of diet, the average duration of observation, the average duration of freedom from advancing caries and the average increment of caries. The data indicate that the median and the average duration of observation far exceed the minimum value defined as a significant period. Further, it is evident that the type response in every subgroup equivocal. The best response was seen in the group studied early on the high fat diet, when the level of supervision and the duration of hospitalization were greater than was possible in the later studies. This same group of children seen later under the lower fat regimen and with lessened supervision showed a group response in relation to the progression of caries which possibly is significantly poorer than that of the other subgroups.

Table 2 has been prepared to permit study and comparison of the diets containing higher and lower amounts of fat. The menus employed have been published heretofore.[2] The values for the compositions of foods were obtained from the manual by Bowes and Church.[3] For purposes of example the contrasted diets for a child of 10 years weighing approximately 70 pounds (31.8 Kg.) have been chosen. The table lists the

TABLE 1.—*Summary of Dental Response to the Ingestion of Different Levels of Fat with Diets of Similar Nutritional Worth*

Nature of Group	Number of Subjects	Duration of Observation, Months		Duration of Freedom from Advancing Caries (per Cent of Total Duration of Observation)			Annual Increment of DMF * Tooth Surfaces		
		Median	Mean	Mode	Median	Mean	Mode	Median	Mean
Total groups of subjects without regard to level of fat ingestion	111	60	67	100	86	78	0.00	0.29	0.71
Children receiving high fat diets only	26	51	54	100	87	75	0.00	0.26	0.72
Children receiving lower fat diets only	39	40	42	100	88	76	0.00	0.31	0.72
Children receiving first high fat, then lower fat diets: high fat period	46	41	48	100	93	84	0.00	0.12	0.58
As in foregoing: lower fat period	46	41	40	100	84	72	0.00	0.31	1.00
All subjects during periods with high fat diet	72	47	50	100	89	82	0.00	0.23	0.63
All subjects during periods with lower fat diet	85	40	41	100	86	74	0.00	0.31	0.87

* DMF indicates decayed, missing or filled.[1c]

was one of absolute or essential freedom from advancing decay and that the typical individual rate of progression of caries was insignificant throughout.

Charts 1 and 2 summarize the data further in terms of the percentile levels of nonprogression of caries and of annual increment of caries. Chart 1 shows that in each of the 4 subgroups there was essentially no advance of caries throughout the period of observation for at least half of the children and that there was no great or constant type of divergence within any subgroup. Chart 2 gives evidence that the degree of extension of caries was even less than the duration of nonadvance would suggest.

When the data in table 1 and in charts 1 and 2 are reviewed from the standpoint of the relative protection against caries afforded by the higher versus the lower fat diets it is noted that such differences as exist bear no constant relationship to the level of fat in the diet. The differences between the values for the groups who received exclusively the higher and the lower fat diets are

nature, weight and analysis of the foodstuffs prescribed for daily consumption. Each patient was allowed a choice of meats, vegetables and fruits; to simplify the table and to permit better comparison, however, specific foods of these classifications have been used in the calculations. Inasmuch as the same foods were used as examples for each of the two diets in so far as possible, errors due to arbitrary selection of foodstuffs have been minimized. The table also permits comparison of the nutritional quality of the diets with the values recommended by the Food and Nutrition Board of the National Research Council.[4]

2. (*a*) Boyd, J. D., and Nelson, M. V.: Diabetic Diets for Children, J. Am. Dietet. A. **2**:45 (June) 1926. (*b*) Boyd, J. D.: Diabetes Mellitus, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1942, vol. 3, chap. 12.

3. Bowes, A. deP., and Church, C. F.: Food Values of Portions Commonly Used, ed. 4, Philadelphia, Philadelphia Child Health Society, 1942.

4. Recommended Daily Allowances, Food and Nutrition Board, National Research Council, Reprint and Circular Series no. 115, 1943.

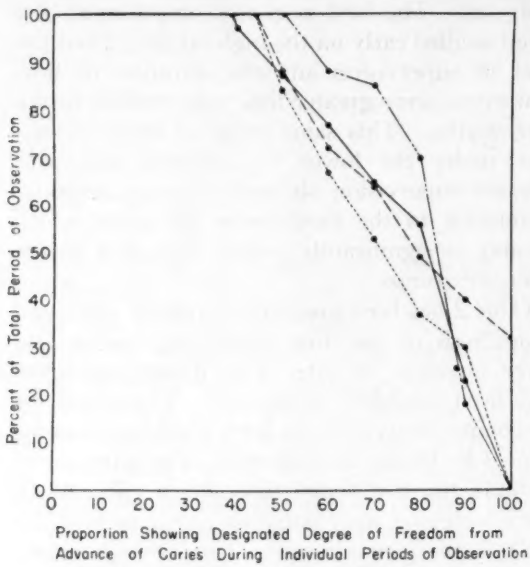

Chart 1.—Cumulative percentage frequency curves relating to duration of nonadvance of dental caries. The total series has been subdivided as follows: children observed solely while receiving a high fat diet (solid line); children observed solely while receiving a lower fat diet (dash line); children observed during an initial period on a high fat diet (line composed of dots and dashes) and children observed while receiving a lower fat diet after an initial period on high fat diet (dotted line).

TABLE 2.—*Composition of Contrasted Diets and Recommendations of National Research Council*

	Prescribed Daily Intake for Child Weighing About 70 Pounds (31.8 Kg.) and About 10 Years Old		Recommendations of National Research Council
	High Fat	Lower Fat	
Calculated Composition of Diets *			
Protein	70 Gm.	70 Gm.	70 Gm.
Carbohydrate	90 Gm.	150 Gm.	
Fat	210 Gm.	110 Gm.	
Potential dextrose	153 Gm.	203 Gm.	
Fatty acid : dextrose ratio	1½:1	1:1½	
Calories	2,530	1,870	2,200
Calcium	1.3 Gm.	1.3 Gm.	1.2 Gm.
Phosphorus	1.5 Gm.	1.5 Gm.	
Iron	11+ mg.	11+ mg.	12 mg.
Thiamine	1.1 mg.	1.3 mg.	1.2 mg.
Ascorbic acid	75+ mg.	100+ mg.	75 mg.
Riboflavin	2.5 mg.	2.9 mg.	1.8 mg.
Nicotinic acid	12+ mg.	11+ mg.	12 mg.
Vitamin A	16,000 U.S.P. units	11,000 U.S.P. units	4,500 U.S.P. units
Vitamin D	600 U.S.P. units	540 U.S.P. units	400+ U.S.P. units
Excess base	+7 cc. N.	+20 cc. N.	
Nature and Amounts of Prescribed Foods, Gm.*			
Milk	525	1,000	
Cream, light	465	...	
Butter	87	55	
Egg	58	65	
Bacon	25	20	
Meat	104	94	
Cereal products	24	68	
Fruits (10% carbohydrate)	120	324	
Vegetables (5 and 10 % carbohydrate)	232	175	
Cod liver oil	4	4	

* Values for composition from Bowes and Church.[3] Similar foods were used for examples in each diet, with some pooling of averages for like types of foodstuffs.

COMMENT

The causation of dental caries is a subject of controversy. Even among the authors who grant the effectiveness of diet in the control of dental decay opinion is divided as to the manner of its effect. Throughout the course of the joint medical-dental studies at the State University of Iowa the view has been held that the normally functioning body has the power to protect the teeth against decay. Prolonged arrest of caries has been seen not only in children receiving so-called "diabetic diets" which were restricted in their sugar content but in nondiabetic children whose controlled diets had a high content of readily fermentable simple sugars for periods of months or years.[5] In all the subjects presenting such control of caries the nutritional regimen was similar, even though the dietetic policies varied widely; all subjects studied received diets as nutritionally complete as knowledge and circumstances permitted. It may be significant that there was no increase in the rate of progression

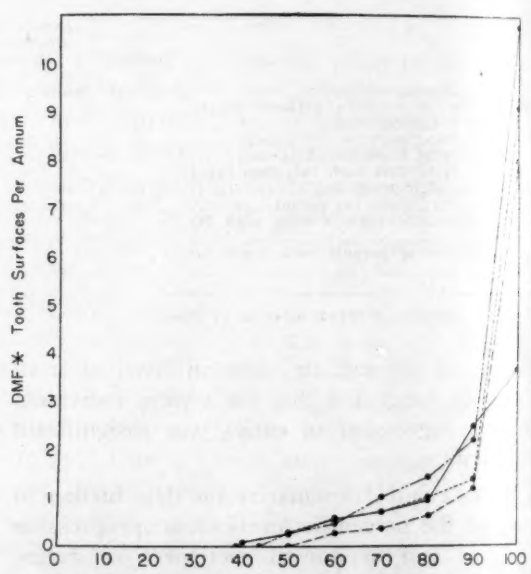

Chart 2.—Cumulative percentage frequency curves relating to the average increment rate of caries (DMF tooth surfaces per annum [1c]). The total series has been subdivided as follows: children observed solely while receiving a high fat diet (solid line); children observed solely while receiving a lower fat diet (dotted line); children observed during an initial period on a high fat diet (dash line), and children observed while on a lower fat diet after an initial period on a high fat diet (line composed of dashes and dots).

of caries in the children reported on in this study even when the carbohydrate content of the diet had been doubled.

5. Boyd, J. D.: Nutrition as It Affects Tooth Decay, J. Am. Dietet. A. **18**:211 (April) 1942.

Chief consideration in this study is directed toward the effect of fat, rather than of carbohydrate, on the course of caries. Commenting on the observations made at the University of Iowa, McCollum [6] has postulated that the high fat of the diabetic diets may serve to coat the surfaces of the teeth with a film which would resist deleterious oral agencies. If such effect were noteworthy one would expect lessening of the protective effect when the fat content of the diet had been reduced by half. The data presented do not substantiate McCollum's premise; neither the level of fat itself nor the ratio of fat to carbohydrate in the diet serves to explain the caries-preventing power of the diets employed.

Further minor distinctions may be made between the two contrasted diets. The earlier diets were unnecessarily high in caloric allowance and led to overweight, especially in the teen-aged girls; the lower fat diets provided larger amounts of fruits and thus tended to supply ascorbic acid in larger amounts than did the high fat diets, and the excess base was greater in the lower fat diets. The similarly low rates of development of dental caries under the contrasted dietary regimens gives evidence that the three differences just named played no great role in themselves in the protection against caries.

Nutritionally the diets were strikingly similar. They were made up largely from the same types of foodstuffs. Each provided ample amounts of milk, eggs, meat, vegetables, fruits and fish liver oil. The prescribed diets throughout approximated or surpassed the levels of nutritional quality recently promulgated by the Food and Nutrition Board of the National Research Council.[4] There is no evidence that the surplus allowance of certain protective factors (notably vitamin A, riboflavin and, in the lower fat diets, vitamin C) was necessary for the avoidance of caries. The similarly high nutritional worth of the two diets is offered as the explanation for their power to prevent dental decay.

6. McCollum, E. V.; Orent-Keiles, E., and Day, H. G.: The Newer Knowledge of Nutrition, ed. 5, New York, The Macmillan Company, 1939, p. 628.

SUMMARY

Dental data previously reported have been reanalyzed to determine whether caries-preventing qualities of diabetic diets properly can be attributed to their content of fat. No constant or significant difference in the average rates of progression of caries was found between two groups of children whose fat ingestion differed by 100 per cent. Protection against caries is thought to depend on the common high nutritive worth of the contrasted diets.

Children's Hospital.

Case Reports

HYDRANENCEPHALY

REPORT OF TWO CASES WHICH COMBINE FEATURES OF HYDROCEPHALUS AND ANENCEPHALY

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The newborn infant gives no evidence that his cerebral hemispheres are functioning, and some writers have likened the infant at this stage to the reflex animal. Two cases recently observed showed that infants without cerebral hemispheres can, in fact, perform nearly all of the activities usually regarded as normal for this period.

REPORT OF CASES

CASE 1.—B. C. S., an infant girl, was the first child of a 23 year old mother. The infant was born at term, the delivery being complicated by a persistent occiput right transverse position, necessitating rotation (Kielland forceps). The weight at birth was 8 pounds 7 ounces (3,840 Gm.). At delivery it was noted that the head was large, that it was considerably molded and that a large caput succedaneum was present over the occipital region, further accentuating the appearance of molding. The child breathed and cried almost at once. Body measurements were as follows: length 21½ inches (54 cm.), occipitofrontal circumference of head 16¼ inches (40.5 cm.) and suboccipitobregmatic circumference 15 inches (37.5 cm.). The heart was beating at the rate of 104 pulsations per minute, with normal tic-tac sounds. The infant was severely jaundiced. The hemoglobin content of the blood was 100 per cent (Sahli), the erythrocyte count 4,000,000 per cubic millimeter and the white cell count 7,650. A differential count of the white cells of the blood on the eighth day of life showed that 25 per cent were polymorphonuclear leukocytes, 5 per cent eosinophils, 56 per cent lymphocytes and 11 per cent monocytes. The red cells showed poikilocytosis and anisocytosis, and there were certain cells of the monocyte series difficult to classify.

Beginning approximately nine hours after birth, the infant was given an evaporated milk formula on a four hour schedule; from ½ to 2 ounces (15 to 60 cc.) was taken fairly well. Sucking and swallowing reflexes seemed to be normal. Body temperature was maintained without assistance throughout the nine days which the infant lived with the exception of two occasions when the temperature was observed to be subnormal (96.4 F.). In general the infant was more quiet and less active than normal newborn infants, but she cried when disturbed and was capable of moving all four extremities in the purposeless, uncoordinated manner characteristic of newborn infants. The child responded to painful stimuli, and closed her eyes when a bright light was flashed. The Moro reflex was present. On the third day of life roentgenograms of the skull showed the presence of a large cranial vault and spreading of the sutures (fig. 1). By cranial tap straw-colored fluid was obtained immediately on penetrating the scalp (in the lateral angle of the anterior fontanel). Four ounces (120 cc.) of this fluid drained readily, before the needle was withdrawn for precautionary reasons. Four days later (on the eighth day of life) cranial tap was again performed, and 220 cc. of fluid was removed from each side of the skull. The fluid was withdrawn in amounts of 50 cc., and equal volumes of oxygen were injected. Roentgenograms taken immediately after this procedure revealed almost complete cerebral agenesia (fig. 2). The removal of fluid caused a decided change for the worse in the condition of the infant; convulsions[1] came on soon thereafter and increased in frequency until the death of the infant the following day.

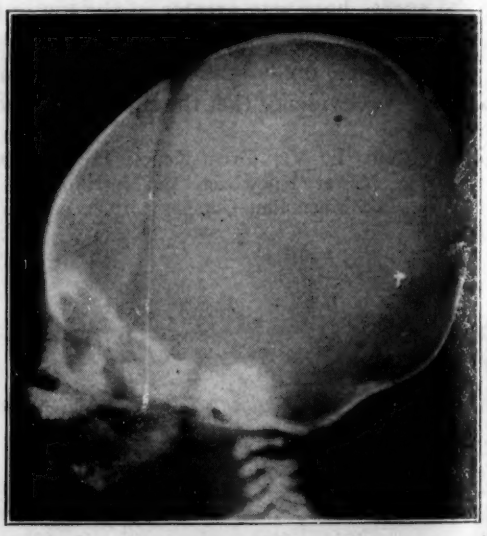

Fig. 1.—Roentgenogram of B. C. S., revealing the anteroposterior elongation and abnormal thinness of the skull, and the unusually wide open sutures and fontanels. Compare this photograph with figure 3.

Postmortem examination revealed two large empty cavities where the cerebral hemispheres are normally located. The falx cerebri was present, and the tentorium was intact. No vestige of cerebral tissue was recognizable on gross examination. Otherwise gross postmorten examination revealed nothing significant. The following report on the detailed structure of the brain

From the Department of Pediatrics and Communicable Diseases, University of Michigan Medical School.

1. An electroencephalogram was not made, but it is certain in this case that convulsions were not the result of electrical stimuli arising in the nonexistent cerebral hemispheres.

was made by Dr. Elizabeth C. Crosby, Professor of Neuroanatomy, University of Michigan Medical School.

"The olfactory bulb and crus were of normal size; the optic nerve was small; the trochlear nerve was not identified, but the remaining cranial nerves appeared grossly normal. Mamillary bodies were present and of normal size. Only portions of the tuber cinereum and the hypothalamus and of the preoptic region immediately adjacent to the optic chiasma were present. The rest of the diencephalon was gone, except the hypophysis cerebri and the pineal body. The latter was partly decomposed or broken down, possibly as a result of postmortem change.

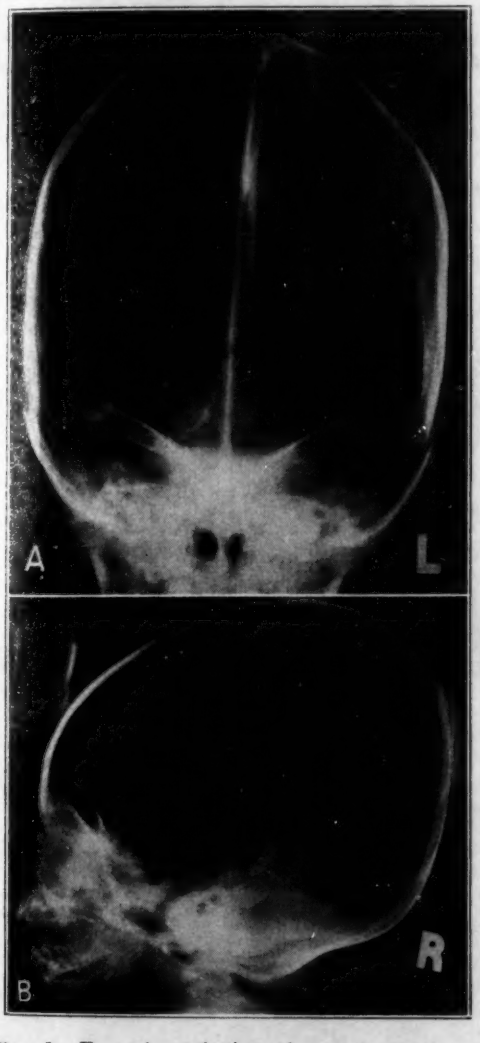

Fig. 2.—Frontal and lateral roentgenograms of B. C. S., after withdrawal of fluid from the cranial cavity and its replacement with oxygen, revealing the absence of cerebral tissue and the presence of the falx cerebri. The base of the cranium appears to be essentially normal.

"The cerebral hemispheres were missing but a primitive outline of them was represented by a thin gray film underlying the pia mater. That this membrane was actually a shell resembling hemispheres became quite apparent when it was filled out loosely with cotton. This reconstruction indicated a stage of cerebral development after an embryonal temporal pole has formed but apparently without the delineation of the sunken island of Reil. A small gray mass, about 1 inch by ¾ inch (2.5 by 2 cm.), was observed at the caudomesial portion of the hemisphere. The gray matter was entirely destroyed; only occasional remnants of a few neurons were encountered; the meninges were thickened, and their vessels were distended; a large primitive choroid plexus was also present. The shape of the falx cerebri suggests that a corpus callosum was once present, but this was the only evidence of such structure.

"The superior and inferior quadrigeminal bodies, forming the roof of the midbrain, were identifiable but ill formed. Grossly no aqueduct was found, but subsequent histologic examination revealed a small cavity lined with ependyma and ending blindly. There was some gross distortion at the base of the midbrain, but the cerebellum, the pons and the medulla were approximately of normal size and shape. There were some slight changes in the upper end of the fourth ventricle and in the surrounding gray matter which could have been due to pressure.

"Throughout the brain there were dilatation of the small vessels and evidence of regions of hemorrhage. The medullation was slightly less than expected in a newborn infant."

Case 2.—The second patient, G. S., was referred to the University Hospital one week after birth, with a diagnosis of hydrocephalus. There was a history of

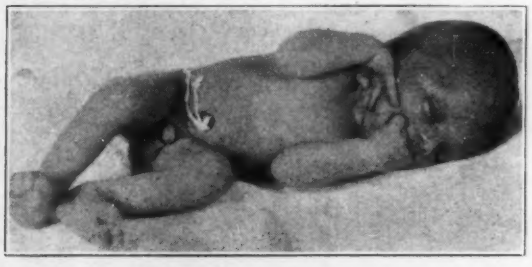

Fig. 3.—This normal-appearing infant, G. S., gave no hint by his actions that he lacked cerebral hemispheres. The other infant here reported on appeared equally normal, but antemortem photographs were not obtained.

difficult, instrumental delivery and some difficulty in initiating respiration, but otherwise the neonatal course to the time of hospitalization was normal. The weight at birth was 3,960 Gm. (8¾ pounds). This infant was the fifth child of a 38 year old mother. The previous pregnancies had resulted in three living children and one stillborn infant. Prior to admission to the hospital the infant had been taking a formula and had gained 1½ pounds (675 Gm.).

On physical examination four things were immediately noted. In spite of a superficially normal appearance (fig. 3) the baby was less reactive and less responsive to manipulation than a normal infant. The head was grossly enlarged and of an unusual shape, best described as egg shaped with the greater enlargement in the occipital area. The infant felt cold to touch, and his temperature was 92 F. at the time of admission to the hospital. There was severe jaundice. The body length was 54 cm.; the weight was 10¼ pounds (4,650 Gm.), and the occipitofrontal circumference of the head was 16¾ inches (41.5 cm.). The fontanels and cranial sutures were widely open and bulging slightly; the cranial bones seemed thin and yielded to pressure; the veins of the scalp were dilated. The

pupils reacted sluggishly to light and the eyes moved in various directions, but the movements of the two eyes were uncoordinated. The eyes closed when a light was flashed in them. The left palpebral fissure appeared to be larger than the right, giving an appearance of protrusion of the left eye; the scleras were deep yellow. The conditions observed in the remainder of the physical examination were essentially normal, and, like patient B. C. S., this infant could move all extremities, was not spastic and seemed little different from a normal newborn child.

On the day of admission to the hospital a puncture of the anterior fontanel disclosed the presence of yellow fluid just beneath the scalp; 45 cc. was allowed to drain off and more could have been removed. No other operative procedures were attempted, as it was obvious that the child had a serious intracranial abnormality which would soon prove incompatible with life. The baby took feedings poorly, and almost constant attention was needed to keep his temperature above

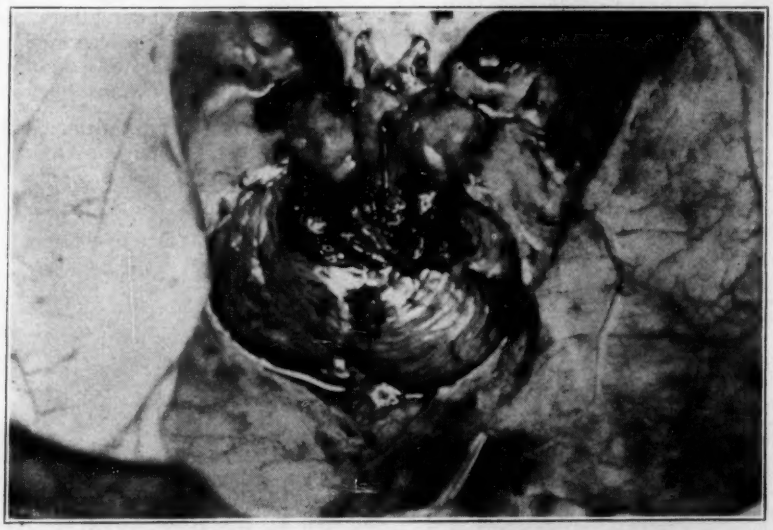

Fig. 4.—Photograph taken after the skull of G. S. had been opened along the suture lines, the segments drawn outward and the falx removed. The view is down into the empty cranium revealing the cerebellum. (The tentorium cerebelli had been removed.) In front of the cerebellum are two light-colored, walnut-sized masses subsequently shown to consist of basal ganglions. Anterior to these, the optic nerves are readily visible.

97 F. Temperatures of 94 F. were recorded on two or three occasions. The infant survived for eighteen days, death being somewhat hastened by aspiration of part of a vomited feeding. Blood counts, urinalysis and examination of the stools yielded normal results. The urine contained a trace of albumin and a few granular casts. On the day after the child was admitted to the hospital (seventh day of life) the hemoglobin content was 140 per cent (Sahli), the erythrocyte count 6,100,000 and the leukocyte count 8,000 per cubic millimeter. A differential count of the white cells showed that 25 per cent were polymorphonuclear leukocytes, 1 per cent basophils, 70 per cent lymphocytes and 4 per cent monocytes.

Postmortem examination revealed apparent complete absence of cerebral hemispheres (fig. 4). The head contained between 500 and 600 cc. of straw-colored fluid. All tissues and organs were stained greenish as part of the intense icterus. The adrenal glands were hypoplastic, and there was hyperplasia of mesenteric lymphoid tissue and of the thymus.

The following detailed description of the brain and brain stem was made by Dr. Konstantin Scharenberg, assistant professor of neuropathology and pathologist in the Neuropsychiatric Institute.

"The central nervous system consisted of the spinal cord, the medulla with an open, wide and malformed fossa rhomboidea, two elongated masses of nerve tissue representing the midbrain and the basal ganglions and finally the cerebellar hemispheres.

"Histologically, the spinal cord was seen to be well developed; the anterior, lateral and posterior horns were well defined and the gray matter was well demarked from the white; there was a distinct central canal lined with ependyma, and the white matter was of normal width. The development of the medulla approximately corresponded to that of the spinal cord. Definitely present were the nuclei of the cranial nerves from the third to the twelfth, the nucleus gracilis, the nucleus cuneatus, the reticulate substance, the nuclei of the raphe, the inferior olives and the external arcuate nuclei; the pyramidal tracts were absent. The nuclei of the pons were present but were irregularly shaped. In the midbrain (fig. 5) the red nuclei, the substantia nigra and the subthalamic nuclei were easily recognized. In the basal ganglions the pallidum and putamen were well developed and showed an almost normal structure (fig. 6). The thalamus was represented by a large, distinct lateral nucleus and by islets of neurons, possibly corresponding to the medial and anterior nuclei. In spite of a careful search a structure corresponding to the hypothalamus could not be traced; this portion of the diencephalon was apparently reduced to a few scattered neurons placed near the third ventricle. The stage of development of the cerebellum corresponded to that in a newborn infant; the granular, Purkinje and molecular layers were well developed, as were also the dentate and tegmental nuclei.

"The cerebral hemispheres were reduced to a small fragment of the allocortex—the cornu ammonis, to which the choroid plexus was attached. The isocortex was not present.

"The development of neurons in all parts of the central nervous system was greatly retarded; the

Fig. 5.—A section through midbrain and pons showing definitely recognizable nuclei and, to the right, the cornu ammonis and a fragment of what is unmistakably choroid plexus: *1*, substantia nigra; *2*, red nucleus; *3*, nucleus of third nerve; *4*, pons; *5*, pulvinar; *6*, cornu ammonis; *7*, temporal lobe; *8*, choroid plexus.

Fig. 6.—A section through the basal ganglions; *1*, a large mass of undifferentiated nerve tissue; *2*, putamen; *3*, pallidum; *4*, red nucleus; *5*, pulvinar.

cells were poorly shaped, the tigroid bodies were broken up and the substance distributed in an irregular fashion throughout the cytoplasm. The nuclei were small and stained poorly."

COMMENT

I have followed Cruveilhier in designating the condition observed in 2 cases reported as "hydranencephaly," using the word which he coined over a hundred years ago. As the word suggests, the condition appears to combine anencephaly and hydrocephalus. Several cases similar to those described here have been reported in foreign medical literature. A case reported by Bettinger [2] appears to have closely resembled the two I have described. Hurowitz [3] described a fetus whose head was so large that craniotomy had to be done to permit delivery. The cerebral hemispheres were missing and were represented by a membrane only. Spielmeyer [4] in 1905 reported this unusual condition in both reported. All showed absence of cerebral hemispheres and imperfect development of the midbrain but presence of an apparently normal pons, cerebellum and medulla.

Study of these 2 cases and of those previously reported appears to eliminate primary nonformation of the cerebral hemispheres as an explanation of the condition. In the case of patient B. C. S. it was possible to reconstruct a semblance of forebrain structures by loosely filling the existing membranes with cotton (fig. 7). In the case reported by Edinger and Fischer the pia mater formed a complete outline or pattern of previously existing cerebral hemispheres. The fact that the infants described in all of these cases had fairly normal-appearing skulls indicates in all probability that the disturbance causing the disappearance of previously formed cerebral hemispheres began rather late

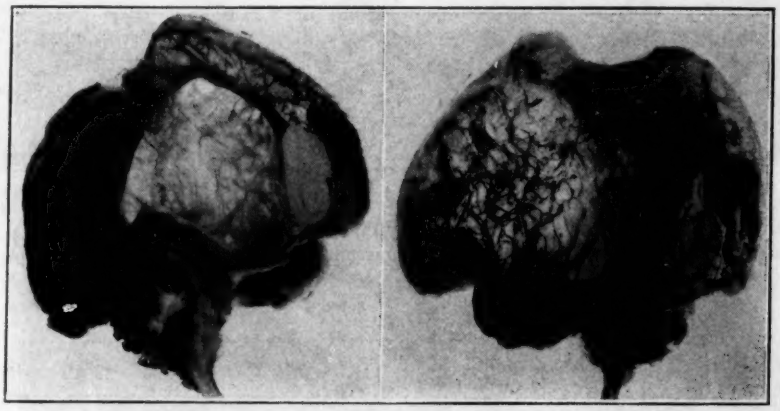

Fig. 7 (Patient B. C. S.).—Hemisection of the membranes, brain and brain stem, showing (left) the essentially normal appearance of all structures except the cerebral hemispheres. The empty membranes outline what appear to be partially developed hemispheres. The specimen to the left was photographed while suspended in a liquid medium and lighted from above and below. Right, the membranes have been loosely stuffed with cotton which brings out their contour. Atypical-appearing temporal and frontal lobes are present.

of nonidentical twins. Edinger and Fischer [5] reported a case in which the cerebral hemispheres had disappeared but the pia mater was present and appeared to have been molded about previously existent hemispheres. In fact, all parts of the contours of normal cerebral hemispheres and corpus callosum were reproduced in cystlike formations. Again the midbrain was imperfectly formed, while lower brain structures were normal.

All of the reported cases have certain features in common with each other and with the 2 herein in fetal development. It was Dr. Crosby's opinion, from study of the case of B. C. S., that the development of the brain was probably normal to at least the fifth month of prenatal development. Thereafter, the forebrain underwent regression. Significant is the fact that the brain of patient B. C. S. showed absence of the aqueduct of Sylvius, which leads to a consideration of the possibility of internal hydrocephalus as the destructive factor. Evidence against the theory that there had been hydrocephalus of a degree sufficient to bring about complete destruction of the cerebral hemispheres is presented by the nearly normal configuration of the skull and the normal condition of the cerebellum and pons. Edinger thought the condition might be the end result of extreme porencephaly, admitting that the idea of such complete destruction

2. Bettinger, H. F.: M. J. Australia **2**:375, 1940.

3. Hurowitz, J.: Schweiz. Arch. f. Neurol. u. Psychiat. **38**:207, 1936.

4. Spielmeyer, W.: Arch. f. Psychiat. **39**:807, 1905.

5. Edinger, L., and Fischer, B.: Arch. f. d. ges. Physiol. **152**:535, 1913.

is difficult to accept. Ibrahim [6] mentioned that Spatz was able to show that newborn animals react differently from adult animals to vascular trauma to the brain. Areas of the central nervous systems of the former liquefy and disappear when the blood supply is interrupted, leaving only cysts or lacunas. In adult animals similar vascular insults result in organization of damaged areas and eventual replacement of these areas by connective tissue.

The duration of life and the degree of development in the cases reported in the literature and my cases are of some interest. The twins described by Spielmeyer, Hurowitz' patient and my patient B. C. S. all lived approximately one week. Patient G. S. lived eighteen days. All of these babies "behaved absolutely the same way as other babies during the first week of life" to quote Bettinger. Most amazing was the infant described by Edinger and Fischer who lived for three and three-fourths years. This infant was breast fed for six weeks and was subsequently fed from a bottle. The child never gave any indication of hunger but slept continuously for the first year and ate only when food was placed in its mouth. The infant would close his eyes to bright light but never followed objects with his eyes; nor did he appear to exercise any of the organs of sense. The child never recognized the mother. Occasionally there were unprovoked fits of screaming which might continue for days.

NOTE.—Since this report went to press postmortem examination of a girl 25½ months old, whose clinical diagnosis was spastic paraplegia, revealed conditions which resembled closely those found in the second of the 2 patients here reported on.

6. Ibrahim, J., in von Pfaundler, M., and Schlossmann, A.: The Diseases of Children, translated by M. G. Peterman, Philadelphia, J. B. Lippincott Company, 1935, vol. 5, p. 153.

PNEUMOPERICARDIUM IN A FORTY-TWO DAY OLD INFANT

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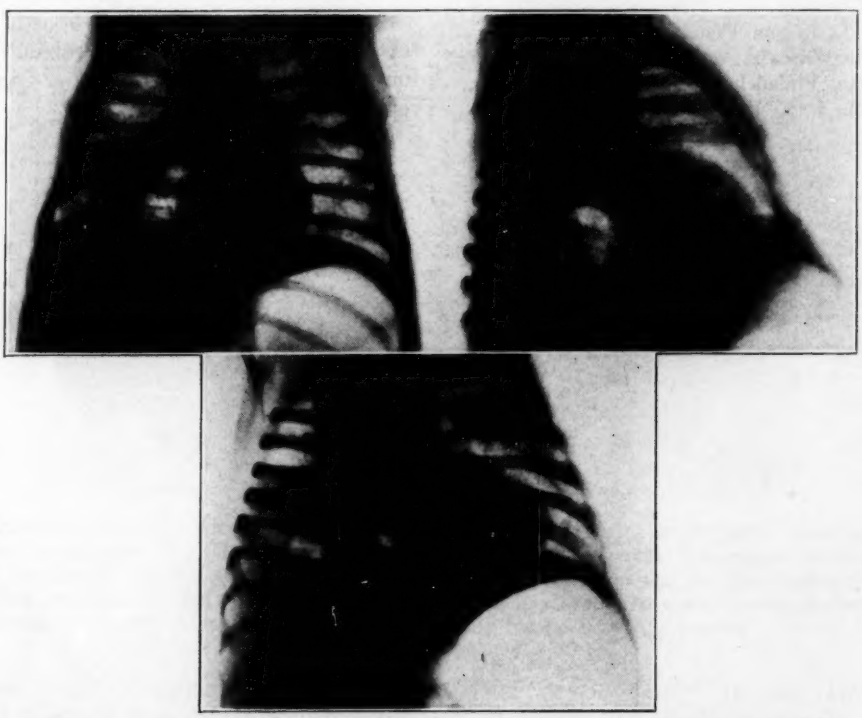
On Aug. 13, 1942 Maria Terezinha, a Negro infant 1 month and 12 days old, daughter of a youthful mother, was admitted to my ward of the hospital. The father was apparently healthy, but the mother during the pregnancy had had a positive Wassermann reaction. She had received antisyphilitic treatment, consisting of injections of a bismuth compound and a total of 8.55 Gm. of neoarsphenamine, in the antepartum clinic. Gestation was normal, and the birth occurred at term, but it was delayed and difficult.* The child was delivered in white asphyxia and was resuscitated by application of artificial respiration, injection of nikethamide and alphalobeline into the umbilical vein and administration of oxygen and carbon dioxide through Draeger's apparatus. As a prophylactic measure vitamin K and 20 cc. of blood were given intramuscularly into the right buttock. The difficult and delayed childbirth was due to the size of the infant. Her measurements were: weight, 3,540 Gm.; length, 52 cm.; biparietal diameter of the head, 10 cm.; occipitofrontal diameter of the head, 11 cm.; cephalic circumference, 34.5 cm.; thoracic circumference, 32 cm., and circumference at the abdominal girdle, 30 cm.

On the day of birth no abnormality in the infant was noted, but on the following day (July 1) the baby showed rigidity of the right arm, refused breast feeding and had difficulty in swallowing. The next day, July 2, there was pronounced paresis of the right leg with talipes equinus, and the plantar reflex was abolished. Roentgen examination of the arm revealed no abnormality, and a lumbar puncture showed that the spinal fluid was clear. On the fourth day the legs were immobilized by splinting and the cord dropped off.

After seventeen days in the hospital the child was discharged in good health, but on the thirty-second day she was readmitted because a small abscess had appeared on the right buttock. The abscess was incised. After ten days of treatment the wound still refused to heal; it increased in size and depth until it became converted into a fistula extending into the rectum. At this stage the baby was transferred to my ward.



Roentgenograms showing pneumopericardium, several pneumonic foci in the parenchyma and two large abscesses in the lower lobe of the right lung.

On September 1 the child had a sudden attack of dyspnea, with quivering nostrils and intense agitation. On auscultation, rough bubbling rales and muffled cardiac sounds were heard. On September 2 a diagnosis of bronchopneumonia was made and sulfapyridine was prescribed.

Because the condition of the child became worse and the temperature remained high, roentgen examination of the chest was requested. The series of roentgenograms which were taken revealed pneumopericardium,

From the Instituto Nacional de Puericultura.

an unusual condition. As the photographs show, a layer of air surrounded the heart, separating the latter from the pericardium and converting the potential space into a real one. The diagnosis of bronchopneumonia was confirmed. Several pneumonic foci were disseminated through the parenchyma and there were two large abscesses in the lower lobe of the right lung, separated from each other by a parenchymatous condensation. A few hours after the second attack of dyspnea the child died.

Postmortem examination revealed scattered pneumonic patches in both lungs. There were two large localized abscesses at the base of the lower lobe of the right lung. The existence of pneumopericardium was demonstrated by the free escape of gas at the moment of incision of the sac. This gas was contained in the pericardium under some tension, which explains the muffling of the cardiac sounds. Moreover, the pathologist found several adhesions between the lung and diaphragm and between the latter and other neighboring organs. No other abnormality was found in the pericardium, and the myocardium was normal. When the larger abscess, which was in intimate contact with the pericardium, was opened it was noted to be in communication with a fairly large bronchial tube. This relationship probably explains the origin of the pneumopericardium. A culture of pus from this abscess gave an exuberant growth of Staphylococcus. The infection in the lung probably originated from the abscess in the gluteal region.

COMMENT

Molnar,[1] in a paper published in 1927, asserted that the presence of gas in the pericardium was extremely rare. Only after the discovery of x-rays were articles on this subject published; the condition had been seen previously only at autopsy. Molnar distinguished two forms of pneumopericardium. In one form, the more common, fluid as well as air is present in the pericardium. The fluid may be serous, purulent or sanguineous, and the condition is termed hydropneumopericardium, pyopneumopericardium or hematopneumopericardium. The prognosis in this form is poor. Hydropneumopericardium can be caused by introduction of air into the pericardium during exploratory puncture in a patient with serous pleurisy (the case cited by Kohlmann[2]) or by opening of the pericardium into neighboring organs that contain air due to one of various causes (for instance, fracture of a rib or opening of an abscess). Molnar cited several examples of this type of pneumopericardium. Graves[2] described an abscess of the liver which opened simultaneously into the stomach and pericardium, and MacDowel[2] reported that in 1 patient a cavity in the lung was the starting point for penetration of germs and air into the pericardium. Jottesman and Bendick[2] described a patient in whom, after necrosis of a gastric carcinoma and formation of a gastropericardial fistula air and gastric contents penetrated into the pericardium. When the pneumopericardium is accompanied with hydropericardium roentgenographic diagnosis is easier. Above, the shadow of the heart is surrounded by a clear area (the layer of air) outwardly limited by the shadow of the pericardium, while the lower part of the pericardial sac, full of fluid, forms a dense shadow, which shows clearly in the roentgenogram. The pulsations of the heart keep the fluid constantly in motion. The second type of pneumopericardium, more rare and more difficult to diagnose, is characterized by the absence of fluid. Molnar[1] stated that the difficulties in diagnosis lie in the fact that the layer of air is not clearly visible with the fluoroscope and that such a rare condition is usually not considered. Good roentgenography is necessary for diagnosis of this type of pneumopericardium. Besides reporting an original case, Molnar[1] cites cases reported by Ljungdahl and Saupe in which pneumopericardium followed therapeutic pneumothorax.

Dr. Corrêa Nunes, of the Department of Radiology, made the roentgenologic studies, and Dr. Newton Potsh provided the clinical history prior to August 13.

Avenue Beira Mar. 152.

1. Molnar, J.: Ueber Luftansammlung im Herzbeutel, Fortschr. a. d. Geb. d. Röntgenstrahlen **36**:656-658, 1927.

2. Cited by Molnar.[1]

ERYTHROBLASTIC ANEMIA OF COOLEY (FAMILIAL ERYTHROBLASTIC ANEMIA) IN AN INDIAN BOY

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From the ill defined group of conditions known as von Jaksch's anemia, Cooley[1] in 1927 separated a type of anemia which occurred in children which he regarded as a clinical entity and which presented characteristic clinical, roentgenologic and microscopic features. He reported that clinically children with this disease exhibited splenomegaly, muddy, yellowish discoloration of the skin and mongoloid facies, due to abnormal prominence of the malar bones. The patients were invariably of Greek, Italian or Syrian stock. Roentgenologically, osseous dystrophy, with thickening and sponginess of the bones, was a characteristic feature; microscopically, there was evidence of hemolytic (hypochromic) anemia, with an unusually large number of nucleated red cells in the blood. Cooley stressed the ancestry of these children, and it came to be believed that this type of anemia was almost exclusively confined to children of Mediterranean stock, so much so that one of the synonyms for familial erythroblastic anemia is Mediterranean fever. Recently its occurrence in persons of other races has been reported but the number of cases is so small that the one reported here, in which the patient was a Brahmin Hindu boy in Bombay, is likely to be of interest.

REPORT OF A CASE

Clinical History.—A Brahmin boy aged 7 years was admitted to the Bai Jerabai Wadia Hospital for Children in Bombay because of intense pallor, enlargement of the head and general debility.

He had been brought to the outpatient department in August 1941 because of general debility following an attack of typhoid (forty-two days' duration). The child was offered admission then, but the parents refused, so he was treated for anemia in the outpatient department. The enlarged head of the child attracted attention, and a roentgenogram was taken. In the differential diagnosis based on the roentgen observations, Cooley's anemia was suggested as a possibility. The diagnosis was later confirmed.

The weight of the patient was 29 pounds (13.2 Kg.) (normal for the age, 42 pounds [19 Kg.]); his height was 39.5 inches (100 cm.) (normal, 49 inches [125 cm.]), and the circumference of his head was 21.5 inches (54.5 cm.) (normal, 20 inches [50 cm.]). The facies of the child showed muddy discoloration, extremely prominent malar bones and well developed epicanthic folds, suggesting a mongoloid character (fig. 1 *A*). The chest was rachitic, the sternum being pushed forward and Harrison's sulcus being evident on both sides (fig. 1 *B*). The lungs showed slight basal congestion. The heart was enlarged to the left and downward, the apex being felt in the seventh left intercostal space in the midclavicular line. A soft systolic bruit, most audible over the apical region, could be heard all over the cardiac area. The abdomen was protuberant (fig. 2). The liver was enlarged to 3 fingerbreadths below the costal margin. The spleen was large, and its margin could be defined 4 fingerbreadths below the costal margin. There was no evidence of free fluid in the abdomen. Both optic disks showed slight pallor. The costochondral junctions did not show any enlargement suggestive of rickets.

Fig. 1.—Photographs of a child with familial erythroblastic anemia. *A* shows the enlargement of the head, prominent malar bones and mongoloid facies; *B* shows Harrison's sulcus.

Roentgenographic Observations.—Roentgenograms of the skull and of the bones of the hands showed a characteristic appearance. The skull was enlarged, and the bones forming the vault were greatly thickened, porous and spongy and had a radiate appearance (fig. 3 *A*). The cancellous part of the bones of the hands and feet was spongy and had a peculiar trabeculated appearance (fig. 3 *B*). The costochondral junctions showed no evidence of rachitic changes.

From the Department of Pathology and Bacteriology, Seth G. S. Medical College.

1. Cooley, T. B.; Witwer, E. R., and Lee, P.: Anemia in Children with Splenomegaly and Peculiar Changes in the Bones: Report of Cases, Am. J. Dis. Child. **34**:347 (Sept.) 1927.

Laboratory Data.—Results of laboratory studies are shown in the following tabulations:

Blood	1/9/42	1/13/42
Erythrocytes,		
No. per cu. mm.	2,200,000	2,160,000
Average size, microns	....	7.7
Fragility, % of NaCl in solution causing lysis	....	0.36 to 0.28 (normal 0.44 or 0.42 to 0.34)
Volume of packed cells,		
Cc. per 100 cc.	15	....
% of normal	35.4	....
Volume index	0.88	....
Saturation index	0.91	....
Mean corpuscular volume, cu. microns	68.2 (normal 87)	....
Mean corpuscular hemoglobin, micromicrograms	23.2 (normal 29.5)	....
Mean corpuscular concentration of hemoglobin, %	34 (normal 35)	....
Reticulocytes, %	7.8	....
Hemoglobin, Gm. per 100 cc.	5.1	4.42
% (Tallqvist)	32.2	28
Color index	0.8	0.72
Icterus index	....	7
Bilirubin (van den Bergh's indirect test)	....	Present
Leukocytes		
Total (including normoblasts), no. per cu. mm.	16,750	35,700
Normoblasts, no. per cu. mm.	7,360	17,521
Other than normoblasts, no. per cu. mm.	9,390	18,179
Polymorphonuclear leukocytes, %	58	71
Neutrophils, %	57	70.5
Segmented, %	48	60
Stab form, %	5	8
Juvenile, %	3	1.5
Myelocytes, %	1	1
Eosinophils, %	1	....
Basophils, %	....	0.5
Mononuclear leukocytes, %	42	29
Lymphocytes, %	38	24.5
Hyaline cells (monocytes), %	4	4.5
Blood parasites	None	None
Cellular abnormalities	Anisocytosis, poikilocytosis and polychromatophilia	Anisocytosis, poikilocytosis and polychromatophilia
Phosphorus, mg. per 100 cc.	....	5.4 (normal 4 to 5)
Calcium, mg. per 100 cc.	....	10.8 (normal 9 to 11)
Kahn reaction	....	Negative

Urine (1/7/42)

Trace of albumin. Excess of urobilin. Occasional red cells and leukocytes.

Gastric Contents (1/6/42)

Sample	Free HCl, Cc.	Total Acid, Cc.	Occult Blood	Bile	Starch	Mucus
Fasting *	0	10	—	—	—	—
¼ hr.	0	11	—	—	+	—
½ hr.	8	16	—	—	—	—
¾ hr.	4	12	+	+	—	—
1 hr.	0	14	+	+	—	—
1¼ hr.	0	10	+	+	+	—
1½ hr.	0	8	+	+	—	—

* No charcoal or lactic acid.

Investigations of Other Members of the Family

In addition to the laboratory studies for the patient, investigations were made on the parents, 2 brothers and 1 sister. It must be noted that the other children were by the first wife, while the patient was a child by the second wife. The two wives were sisters. The Kahn and Wassermann reactions of the parents were negative. The icterus index, van den Bergh reaction and fragility of red cells were studied in the brothers and sister with the following results:

Fig. 2.—Photograph of a child with familial erythroblastic anemia, showing the protuberant abdomen.

Subject	Age, Yr.	Icterus Index	Bilirubin, van den Bergh Test	Fragility of Red Cells, % of NaCl in Solution: Initiating Lysis	Completing Lysis
(E) Boy	13	1	None	0.4 to 0.45	0.3
(D) Boy	10	Hemolysed	None	0.4 to 0.45	0.3
(S) Girl	8	3	None	0.4 to 0.45	0.3

The laboratory data tabulated leave no doubt that this was a typical case of Cooley's erythroblastic anemia.

COMMENT

Koch and Shapiro [2] collected 18 cases from the literature and added 5 of their own. Nearly all

2. Koch, L. A., and Shapiro, B.: Erythroblastic Anemia: Review of Cases Reported Showing Roentgenographic Changes in Bones and Five Additional Cases, Am. J. Dis. Child. 44:318 (Aug.) 1932.

of the cases were reported from the United States, and most of the patients were of Mediterranean stock, of Italian, Greek or Syrian ancestry. The condition has been reported as occurring in an English child only once. Coelho [3] described this type of anemia in 2 sisters aged 6 and 9 years Patel and Bhende [4] published a report of a case in which the patient was a Brahmin boy, aged 5, who had erythroblastic anemia complicated by cirrhosis of the liver and kyphosis. Napier, Shorten and Das Gupta [5] described Cooley's anemia in a Hindu boy aged 10 years. They remarked that they had been unable to find any reference to this disease in persons of Asiatic origin. Although Coelho [3] and Patel and Bhende [4] described their cases earlier, the reports do not appear to have attracted sufficient attention.

Of 5 patients with this disease in India, 3 were boys and 2 were girls. Vaughan [6] mentions that brothers and stepsister of my patient were investigated, but no evidence of any hereditary taint was obtained.

Vaughan [6] mentions that in the 1 instance in which the gastric contents were analyzed no free hydrochloric acid was found after the patient had eaten either an ordinary or an alcoholic test meal. Coelho's patients had no free gastric hydrochloric acid. In Napier's patient free hydrochloric acid was present in the fasting sample of gastric juice equivalent to 20 cc. of tenth-normal sodium hydroxide. Further samples were not examined. Although the fasting sample from my patient did not contain free hydrochloric acid, two of the seven quarter-hour samples examined contained a small amount.

The blood picture in erythroblastic anemia shows a leukoerythroblastic reaction which occurs in diverse conditions, such as Cooley's anemia, chronic hemolytic jaundice, acholuric

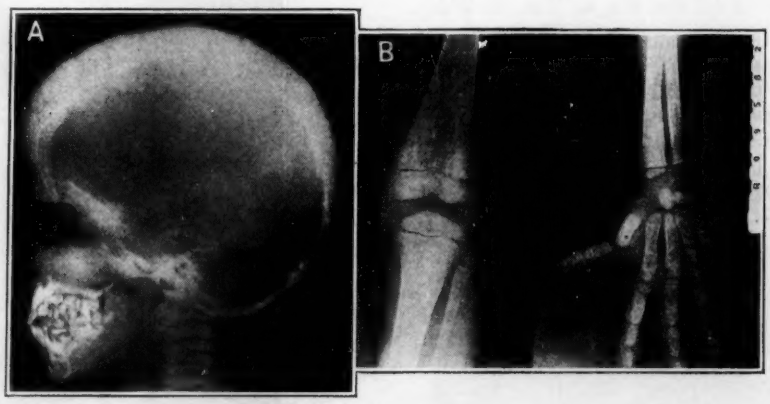

Fig. 3.—Roentgenograms showing the skeletal changes in familial erythroblastic anemia. *A* shows the thickening of the skull and the characteristic radiate appearance of the bones of the vault; *B* shows the sponginess and trabeculation in the bones of the leg, hand and forearm.

in 50 recorded instances the disease occurred more often in girls than in boys.

At least 10 patients have had brothers and sisters who were affected (Koch and Shapiro [2]). Two instances of the occurrence of erythroblastic anemia in identical twins have been recorded (Whipple and Bradford [7]). The stepfamilial jaundice, idiopathic steatorrhea (celiac disease), sickle cell anemia, aleukemic myeloid leukemia, myelomatosis, myelosclerosis, carcinomatosis and osteopetrosis (Albers-Schönberg disease). Although the blood picture is not specific for familial erythroblastic anemia, it is of importance, because in many instances it has helped in drawing attention to this disease in children.

Of greater diagnostic value for this condition are the changes in the bones, but they too are found in other types of anemia. For example, Vogt and Diamond [8] studied 19 cases of anemia in which the roentogenograms of the bones had the appearance typical of this condition; 5 of the cases were of congenital hemolytic anemia, 1 of

3. Coelho, G.: Erythroblastic Anaemia — Cooley's Anemia? M. Bull., Bombay **7**:291, 1939.

4. Patel, N. D., and Bhende, Y. M.: Erythroblastic Anaemia with Kyphosis and Cirrhosis of Liver, Indian J. Pediat. **6**:217 (Oct.) 1939.

5. Napier, L. E.; Shorten, J. A., and Das Gupta, C. R.: Cooley's Erythroblastic Anaemia, Indian M. Gaz. **74**:660 (Nov.) 1939.

6. Vaughan, J. M.: The Anaemias, ed. 2, New York, Oxford University Press, 1936.

7. Whipple, G. H., and Bradford, W. L.: Racial or Familial Anemia of Children Associated with Fundamental Disturbances of Bone and Pigment Metabolism (Cooley-von Jaksch), Am. J. Dis. Child. **44**:336 (Aug.) 1932.

8. Vogt, E. C., and Diamond, L. K.: Congenital Anemias, Roentgenologically Considered, Am. J. Roentgenol. **23**:625 (June) 1930.

sickle cell anemia and 13 of erythroblastic anemia. Vogt and Diamond referred to work by Williams,[9] who made the interesting observation that symmetric osteoporosis was found in the skulls of many pre-Columbian Peruvians and of some North American Indians. This observation suggests an interesting possibility, that is, that one of the reasons for the disappearance of the Mayan Indians was that they were generally affected by some anemic condition allied to congenital anemia.

The changes in the bone are a result of the reaction of the marrow to prolonged overstimulation as a consequence of chronic hemolysis, beginning before the cortex is too firm to permit overgrowth of the marrow. The pronounced striation indicates replacement of the exhausted marrow by new bone, as found in autopsies. Similar changes are not found in the skulls of persons with nonhemolytic anemia, rickets or syphilis.

The question arises as to the cause of hemolysis in anemia of the type described by Cooley. Unfortunately there is no definite knowledge in regard to this. In the opinion of Cooley and Lee[10] there is a primary dysfunction of the metabolism of blood in which hemolysis is a secondary factor. In the opinion of others there is a congenital defect in the formation of red cells resulting in the production of erythrocytes which probably qualify for hemolysis more quickly than do ordinary cells.

William Damashek described a condition, called by him "target cell anemia," in which the red cells are thinner than usual, with a slight thickening in the concavity of the biconcave disks and a bull's-eye or target cell appearance. These cells are more resistant than normal cells to hypotonic solutions. Damashek stated the belief that target cells constitute a congenital anomaly. In the case herein described, the red cells were more resistant to hypotonic solutions of sodium chloride, as shown by the result of the fragility test. On the other hand, in acholuric jaundice the cells are thicker, appearing as spherocytes, and their resistance to hypotonic saline solutions is less than normal. They are more fragile. Cells of both these types are abnormal and, irrespective of their fragility or resistance in vitro, probably succumb earlier in vivo to normal processes of hemolysis. Damashek[11] described target cell anemia in an Italian youth in whom the skeletal changes were similar to those in Cooley's anemia. He has mentioned that, just as splenectomy is of no avail in Cooley's anemia, it does not help patients with target cell anemia. It is worth mentioning, as a point of distinction, that in congenital acholuric jaundice in which such skeletal changes do occur, the red cells are more fragile and splenectomy improves the condition of the patient. I looked for target cells in the blood of my patient but did not find them.

Dr. M. V. Sant, M.S., brought this case to my attention, and Dr. R. N. Cooper, M.S. (London), F.R.C.S. (England), superintendent of Bai Jerabai Wadia Hospital for Children, made possible the publication of the report of the case.

Seth G. S. Medical College

9. Williams, H. U.: Human Paleopathology, with Some Original Observations on Symmetrical Osteoporosis of the Skull, Arch. Path. **7**:839 (May) 1929.

10. Cooley, T. B., and Lee, O. P.: Erythroblastic Anemia: Additional Comments, Am. J. Dis. Child. **43**: 705 (March) 1932.

11. Damashek, W.: "Target Cell" Anemia: Anerythroblastic Type of Cooley's Erythroblastic Anemia, Am. J. M. Sc. **200**:445 (Oct.) 1940.

Progress in Pediatrics

MYOCARDITIS IN CHILDREN

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With the exception of myocarditis in rheumatic heart disease and myocardial degeneration associated with diphtheria, myocardial disease in children has received scant attention.

The meager literature on the subject of myocarditis reveals a wide divergence of opinion. Some authors maintain that myocarditis in children is rare except in association with rheumatic fever and diphtheria [1]; other authors state that, though rare as a primary disease it is common as a secondary disorder in acute infectious diseases.[2] Still others believe that the most important lesion in connection with carditis is myocarditis.[3] Gibson [4] recently stressed that from the standpoint of causation the majority of cardiac ailments fall into four groups: congenital anomalies of the heart, rheumatic heart disease, cardiovascular syphilis and degenerative lesions. Mention was also made of acute and subacute bacterial endocarditis. It is interesting that rheumatic heart disease was referred to as such but that myocarditis as an entity was not mentioned in this connection.

Although it is obvious that there are controversial opinions, the belief generally expressed, based on clinical experience, is that infectious diseases, with the exception of rheumatic fever and diphtheria, rarely produce any serious changes in the myocardium. At autopsy, however, myocarditis of varying degrees of severity is found more frequently than this clinical concept would lead one to expect.

For some time past we have been interested in the occurrence of myocarditis in children, with the thought that perhaps more concerted effort by the pediatrician and the pathologist might clarify the concept of myocarditis in children and bridge the gap between the clinician, who diagnoses myocarditis rarely, and the pathologist, who finds it so much more frequently.

There have appeared in the more recent literature isolated reports of special forms of myocarditis, but systematic studies are lacking.[5] Thus we have been able to find few data on such subjects as the incidence of myocarditis in children and the comparative frequency of occurrence of myocarditis in children and in adults. Likewise there are scant data on record relative to the frequency with which myocarditis is associated with other diseases.

This study is based on an examination of the hearts of 97 children and on an evaluation of the clinical records of these patients. The diagnosis of myocarditis was made histologically in every instance. It should be pointed out that the diagnoses were made in routine examinations and that the hearts were not systematically searched for evidence of myocarditis. It should also be emphasized that in every instance the myocarditis was unquestionably an inflammatory reaction within the myocardium, a true myocarditis. Reparative changes, sometimes erroneously called "myocarditis," were not included, except in an instance in which such "reparative" myocarditis was encountered in a patient with diphtheria. The 97 instances of myocarditis are analyzed, and the recent references available on the subject are reviewed. Particular stress was laid on causation and an attempt was made to decide whether the myocarditis was a complicating factor of the disease, an entity in itself causing death or a purely incidental condition.

The scope of this study embraces the myocarditides observed in a general hospital for chil-

This study was aided by a grant from the Kunstadter Pediatrics Fund.

From the Department of Pathology of Michael Reese Hospital and the Sarah Morris Hospital for Children.

Research in the Department of Pathology of Michael Reese Hospital is in part supported by the Michael Reese Research Foundation.

1. Holt, E., Jr., and McIntosh, R.: Holt's Diseases of Infancy and Childhood, ed. 10, New York, D. Appleton-Century Company, Inc., 1933.

2. Griffith, G. P. C., and Mitchell, A. G.: The Diseases of Infants and Children, ed. 3, Philadelphia, W. B. Saunders Company, 1933.

3. Sutherland, G. A.: Diseases and Disorders of the Heart, in Thursfield, H., and Paterson, D.: Diseases of Children, ed. 2, New York, William Wood & Company, 1929.

4. Gibson, S.: The Cardiovascular System, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1942.

5. Saphir, O.: Myocarditis: A General Review, with an Analysis of Two Hundred and Forty Cases, Arch. Path. **32**:1000 (Dec.) 1941; **33**:88 (Jan.) 1942.

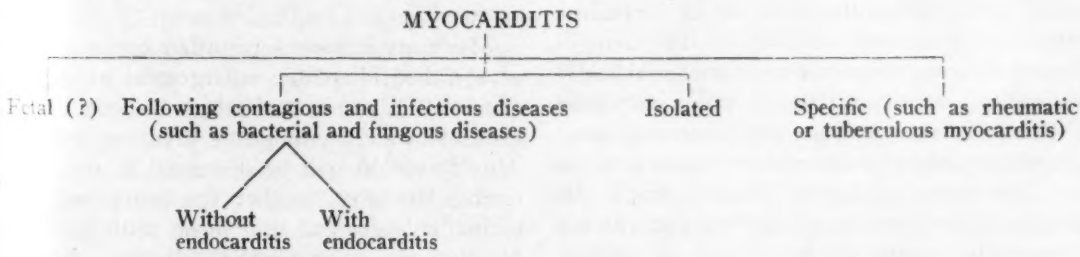
dren. Thus, types of myocarditis occurring during the course of contagious diseases are not included in this series, but reference is made to such data found in the literature.

As previously stated, our material comprises reports on 97 autopsies. However, complete clinical records of only 60 of the patients were available for study.[6] The ages of the children ranged from 8 days to 16 years. There were 18 children under 1 year of age. Nineteen children were between 1 and 5 years old (inclusive); 26 children were between the ages of 6 and 10 years, and 34 were between 11 and 16. Sixty-one were boys, and 36 were girls. Ninety-four were white children, and 3 were Negroes.

These 97 instances of myocarditis were found in 1,420 autopsies on children between the ages of 8 days and 16 years. Thus the incidence of myocarditis in children in a general pediatric hospital, as proved by postmortem examination, was 6.83 per cent. Vischer[7] in 1924 stated that in 793 autopsies on children up to 15 years of age myocarditis was found 27 times, that is, in about 3 per cent. In our material myocarditis was about twice as common as in Vischer's. However, the figures are not completely comparable. Vischer's group was composed of children from birth to 15 years of age, while our material included children from 9 days to 16 years of age.

In comparing the incidence of myocarditis in children and in adults, it may be stated that during the same period of time that these 97 instances of myocarditis were found in 1,420 autopsies on children, 150 instances of myocarditis were found in 3,712 autopsies on adults over 16 years of age, a frequency of 4.05 per cent. The incidence of myocarditis in children in our study, therefore, is distinctly higher than that observed in adults.

Classification of the types of myocarditis is difficult. It is realized today that the old division into parenchymatous and interstitial myocarditis is not justifiable. Brown and Hunt[8] classified myocarditis as acute, syphilitic and tuberculous. Acute myocarditis was subdivided into nonspecific and rheumatic types. Vischer[7] classified myocarditis as follows: acute circumscribed interstitial inflammation (abscesses of the myocardium are included in this group) and acute diffuse interstitial inflammation. The latter may be (*a*) nonspecific, following infectious diseases, (*b*) specific, in rheumatic fever, pertussis, tuberculosis or syphilis, (*c*) the principal disease or an incidental condition in other diseases (in tonsillitis or in phlegmonous inflammation without sepsis) or (*d*) isolated acute diffuse myocarditis (this again is subdivided into the type in which the culture of blood is positive and that in which it is negative). Marshall[9] classified infective myocardial disease into (1) specific myocarditis (rheumatic, tuberculous, gummatous), (2) nonspecific, toxic myocarditis (in diphtheria and other fevers), (3) septic myocarditis (in septicemia and in association with bacterial endocarditis) and (4) isolated myocarditis. For didactic purposes the following classification of myocarditis was previously devised.[5]



The fault of such a classification is immediately obvious. It is evident that rheumatic myocarditis, the result of rheumatic fever, is almost invariably associated with endocarditis. Thus, it can be classified under infectious diseases associated with endocarditis or under specific myocarditis. Nevertheless this classification, while by no means complete or nonoverlapping, seems adequate for didactic purposes and was found suitable for our present study.

In 1 of the 97 instances of myocarditis in our series the condition was diagnosed as postdiphtheritic inflammation of the myocardium. Myocarditis was found in association with meningitis 4 times, with poliomyelitis 7 times, with bronchopneumonia 12 times, with lobar pneumonia 3

6. The staff of the Sarah Morris Hospital for Children, of the Michael Reese Hospital, made possible the use of these records.

7. Vischer, M.: Beiträge zur Myokarditis im Kindesalter, in Czerny, A.: Abhandlungen aus der Kinderheilkunde und ihren Grenzgebieten, Berlin, S. Karger, 1924.

8. Brown, G. E., Jr., and Hunt, H. F.: A Pathological Classification of Diseases of the Myocardium, Am. J. Clin. Path. **10**:540, 1940.

9. Marshall, R.: Some Aspects of Myocardial Disease, Ulster M. J. **11**:69, 1942.

times and with nephritis 3 times. Abscesses in the myocardium were present in 16 instances, associated with various infectious diseases and with various portals of entry. Myocarditis was associated with bacterial endocarditis 5 times and with subacute bacterial endocarditis 7 times. There were 13 instances of a "rheumatic type" of myocarditis. We wish to note here, as it is emphasized later, that by "rheumatic type" of myocarditis is meant inflammatory changes within the myocardium which may or may not resemble Aschoff bodies but which are not typical enough to be classified as such. These changes were found in hearts with endocardial lesions which could have been rheumatic in origin. The changes in the myocardium, however, were not sufficiently characteristic to warrant making the specific diagnosis of "rheumatic" myocarditis. True rheumatic myocarditis was present 19 times. Isolated myocarditis was encountered 3 times, and myocarditis in tuberculosis was found 4 times.

FETAL MYOCARDITIS

Reports on fetal (congenital) myocarditis, except in congenital syphilis, are exceedingly rare. Such reports are found chiefly in the older literature (Abbott [10]). The few references on record, aside from those reporting syphilitic lesions, are concerned with myocardial changes in hearts showing congenital anomalies. Abbott [11] specifically mentioned that in pulmonary and aortic atresia myocarditis, with resulting scarring, was usually encountered in the wall of the conus just below the valve. Von Zalka,[12] who examined 16 hearts with either fetal endocarditis or congenital anomalies, found foci of lymphocytic infiltration and proliferation of connective tissue in both groups. There was perhaps more overgrowth of connective tissue in the second group. Though the differences were slight, he suggested that histologic examination may offer a clue as to whether a congenital anomaly is a result of intrauterine inflammatory changes of the endocardium or a primary malformation.

In the autopsies recorded at Michael Reese Hospital 78 congenital anomalies of various types were encountered. Minor anomalies, such as patent foramen ovale and patent ductus arteriosus, are not included. In several hearts an increase in connective tissue was found but neither acute nor chronic inflammation was observed. There were several earlier records of patients for whom a diagnosis of congenital endocarditis had been made. However, as a result of a restudy of the hearts with so-called congenital endocarditis, the conclusion was reached that the valvular deformities were definitely not the result of primary inflammatory changes but signified the persistence of an early developmental stage of the involved valve. Gross [13] recently stated that the valvular changes seen in such instances were best explained on the basis of developmental defects. In our series none of the hearts with valvular deformities showed any evidence of inflammatory changes in the myocardium. Gross also stated that the myocardial lesions seen in hearts with so-called fetal endocarditis were not inflammatory in origin but represented healed bland infarcts.

Though it is well known that children with severe congenital cardiac anomalies may get along surprisingly well, occasionally death occurs suddenly. Intriguing as it may be to assume that myocardial changes are the direct cause of death in such children, a careful histologic study of a number of such hearts disclosed no evidence of any anatomic lesion in the myocardium to which death at that particular time could be ascribed.

There are instances recorded in the literature of so-called idiopathic enlargement of the heart (Stoloff [14]), in some of which the condition has been associated with status thymicolymphaticus. This condition will be discussed in more detail later. However, neither the hearts with idiopathic enlargement nor those with infiltration by glycogen (von Gierke's disease) show any primary inflammatory changes in the myocardium.

From the literature and from our study of the myocardium of a number of hearts with congenital anomalies, it must be concluded that, with the exception of myocarditis in congenital syphilis, fetal or congenital myocarditis, if it occurs at all, is extremely rare.

MYOCARDITIS IN CONTAGIOUS AND INFECTIOUS DISEASES

As previously stated, the material on which this study is based contains only a few observations on children with contagious diseases, since the observations were made in a general pediatric

10. Abbott, M. E.: Congenital Cardiac Disease, in Osler, W.: Modern Medicine, Philadelphia, Lea & Febiger, 1908, vol. 4, p. 323.

11. Abbott, M. E.: Atlas of Congenital Cardiac Disease, New York, American Heart Association, 1936.

12. von Zalka, E.: Histologische Untersuchungen des Myokards bei kongenitalen Herzveränderungen, Frankfurt. Ztschr. f. Path. **30**:144, 1924.

13. Gross, P.: Concept of Fetal Endocarditis: A General Review with Report of an Illustrative Case, Arch. Path. **31**:163 (Feb.) 1941.

14. Stoloff, E. G.: So-Called Idiopathic Enlargement of the Heart in Infancy and Childhood, Am. J. Dis. Child. **36**:1204 (Dec.) 1928.

hospital. However, the pertinent data in the literature will be summarized and several observations cited.

Diphtheria.—While changes in the myocardium of persons with diphtheria are encountered and recognized clinically as well as anatomically, there still is controversy as to the nature of the lesions. Hoyne and Welford [15] emphasized that the death of every patient with diphtheria who came to autopsy was accounted for on the basis of severe myocarditis. These authors stated that the essential changes were toxic parenchymatous degenerations. Burkhardt, Eggleston and Smith [16] maintained that various degrees of degeneration of muscle fibers, culminating in necrosis, were associated with interstitial myocarditis. Albert [17] could not decide whether the inflammatory or the degenerative changes were primary. Warthin's [18] conclusions perhaps best explain the state of the myocardium in diphtheria. He stated that the essential lesion was a toxic, parenchymatous hyaline degeneration or necrosis, associated with fatty degeneration and cloudy swelling or simple necrosis. Later there occurs a reparative inflammatory process, myocarditis. It is questionable, however, whether Warthin was justified in calling this reparative inflammation true myocarditis.

Clinically, Burkhardt and his co-workers found a rough parallelism between the degree of change in the conducting system as measured by the electrocardiogram and the severity of the histologic changes in the myocardium. However, there was a distinct lack of correlation between the electrocardiographic changes and the demonstrable lesions in the conductive tracts. Chiari [19] described a peculiar configuration of the diphtheritic heart, characterized by a dilatation of the pulmonary conus. This may perhaps be recognized in roentgen examination.

Signs of heart failure may occur at a time when the local inflammation has subsided. Among 23 patients discussed by Albert,[17] the hearts of 4 had "clean" mucous membranes, while in those of 2 patients no change whatsoever could be demonstrated at autopsy. Albert also emphasized sudden death in diphtheria and reported that, though changes in the myocardium were invariably present, nothing was found microscopically to which the sudden death at that particular time could have been ascribed.

There are instances on record in which myocardial insufficiency and sudden death were explained on the basis of old myocardial changes which were believed to have resulted from a diphtheritic infection which the patient allegedly had had a number of years before. In Dusso's [20] case the interval was sixteen years. It is questionable whether one is justified in assuming that the hyalinization of muscle fibers as described by Dusso, even in the heart of a patient with a previous history of diphtheria, is the result of diphtheritic myocardial changes.

The following is an instance of death resulting from postdiphtheritic subacute (reparative) myocarditis. The patient, a 7 year old girl, was admitted to the hospital with difficulty in swallowing and in breathing and severe cyanosis, which had developed one month after a diagnosis of diphtheria had been made. The child had previously been treated at a hospital for contagious diseases. On admission the patient was lethargic, restless and severely cyanotic; respiration was shallow. The pulse rate was 140 to 152 per minute. The temperature at that time was 99.4 F., but before the patient died it rose to 105.8 F. There was a purulent discharge in the pharynx. The cough reflex was weak. The lungs were resonant on percussion and clear on auscultation. The heart was slightly enlarged to the left, and a soft systolic murmur was heard over the apex. All deep reflexes were absent. The patient became more cyanotic, and gradually the cardiac impulse became imperceptible. In spite of the use of the Drinker respirator and the administration of oxygen and cardiac stimulants, the patient died in deep cyanosis. At autopsy the heart was slightly enlarged and pale gray, and the right ventricle was particularly dilated and soft. The epicardium was smooth. The myocardium was grayish purple and of a peculiar, glistening appearance. The valvular apparatus was intact. Examination of the medulla oblongata and spinal cord disclosed much demyelination. Microscopic sections of the myocardium showed swollen muscle fibers which appeared homogeneous and had no striations. Throughout the interstitial tissue a number of inflammatory cells were noted, principally lymphocytes, with a few eosinophilic

15. Hoyne, A., and Welford, N. T.: Diphtheritic Myocarditis, J. Pediat. **5**:642, 1934.

16. Burkhardt, E. A.; Eggleston, C., and Smith, L. W.: Electrocardiographic Changes and Peripheral Nerve Palsies in Toxic Diphtheria, Am. J. M. Sc. **195**: 301, 1938.

17. Albert, Z.: Changes of Myocardium in Children in Infectious Diseases, Nowiny lek. **50**:565 and 619, 1938.

18. Warthin, A. S.: The Myocardial Lesions of Diphtheria, J. Infect. Dis. **35**:32, 1924.

19. Chiari, H.: Ueber Myocarditis, Wien. klin. Wchnschr. **46**:1137, 1933.

20. Dusso, R.: Miocarditi croniche giovanili postinfettive apparentemente primitive a sinto matiche e ad esito infausto, Gior. veneto di sc. med. **10**:337, 1936.

leukocytes and a moderate number of polymorphonuclear leukocytes.

Thus a patient whose illness one month previously was diagnosed as diphtheria was admitted to the hospital with heart failure and respiratory distress. The heart at autopsy showed degenerative lesions, with some necrosis in the myocardium, combined with inflammatory changes. It seemed that the degenerative lesions were primary and that the inflammation was the result of the degeneration and necrosis of muscle fibers. This is a reparative process, not true myocarditis.

Measles.—There are few references available in recent literature on myocardial changes in the hearts of patients with measles. Albert [17] stated that not only slightly inflammatory infiltrations but extensive infiltrations are sometimes seen microscopically in such hearts. These changes, however, are not found before the ninth day of the disease. Of 10 hearts of patients with measles 2 showed myocardial lesions, 3 had foci of pericarditis and 5 revealed no abnormality.

Degen,[21] from a microscopic examination, stated that only 4 of 91 hearts had cellular infiltrations in the myocardium, including 2 with exudative pericarditis. Strong [22] emphasized that the heart is not involved as commonly in measles as it is in other infectious diseases, although occasionally tachycardia or disturbance of rhythm may be noticed during the course of the disease. From these few references it seems that myocarditis in measles is rarely encountered.

Mumps and Whooping Cough.—Myocarditis seems to be a rarely observed complication of mumps and whooping cough. The sudden death due to myocarditis of a patient with mumps was reported by Manca.[23] The older literature includes whooping cough as a causative factor in myocarditis (Kirch [24]). Oberndorfer [25] (1914) demonstrated myocarditis in a 7 year old girl who died suddenly a few weeks after having contracted whooping cough. There were many infiltrations of round cells throughout the myocardium. Among the previously mentioned 27 cases of myocarditis reported by Vischer,[7] there was 1 in which the patient was a 4½ year old girl for whom a clinical diagnosis of whooping cough and endocarditis was made. At autopsy, however, Vischer observed no evidence of endocarditis but an interstitial myocarditis with predominating lymphocytes, a few leukocytes and plasma cell–like cells.

Scarlet Fever.—Toomey [26] stated that 5 per cent of patients with scarlet fever have demonstrable cardiac enlargement, which may be transitory. However, a few of his patients had persistent tachycardia. One child, who died with complicating sepsis, had abscesses in the myocardium. Another child, in whom heart block had developed during life, had petechial hemorrhages in the bundle of His. Albert [17] studied the hearts of 8 children with scarlet fever, 4 of whom had myocarditis. The hearts of 2 of 5 patients with scarlet fever combined with diphtheria showed small foci of myocarditis. Stoeber,[27] who had observed a number of young persons with myocarditis due to scarlet fever, stated that clinically myocarditis may occur as early as the third or fourth day of life. In the patients observed by him, usually the heart was enlarged to the left and a soft systolic murmur was audible. The pulse rate was slow, and there was evidence of arrhythmia. The latter condition is explained on the basis of inflammatory changes within the conducting system. Stoeber emphasized that sometimes sudden death in scarlet fever may be related to these changes. Because of the fact that scarlet fever is sometimes complicated by rheumatic fever, Aschoff bodies may be found in the myocardium of patients dying from scarlet fever, though Aschoff bodies are never found in the myocardium of patients with uncomplicated scarlet fever.

Stegemann [28] emphasized the presence of inflammation within the stroma of the cardiac ganglions. He believed that these changes might be the cause of death of severely toxic patients.

The studies of Brody and Smith [29] are interesting because they showed that careful microscopic examination of the heart revealed changes in a higher percentage of cases than is generally

21. Degen, J. A., Jr.: Visceral Pathology in Measles: A Clinicopathologic Study of One Hundred Fatal Cases Am. J. M. Sc. **194**:104, 1937.

22. Strong, R. A.: Measles, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1942, vol. 2.

23. Manca, C.: Myocardite da parotote epidemica, Arch. ital. di anat. e istol. pat. **3**:707, 1932.

24. Kirch, E.: Pathologie des Herzens, Ergebn. d. allg. Path. u. path. Anat. **22**:1, 1927.

25. Oberndorfer: Pathologisch-anatomische Demonstrationen, Monatschr. f. Kinderh. **13**:356, 1914.

26. Toomey, J. A.: Scarlet Fever, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1942, vol. 2.

27. Stoeber, E.: Ueber Myokarditis bei Jugendlichen, besonders Scharlach Myokarditis, Arch. f. Kinderh. **105**:193, 1935.

28. Stegemann, A.: Die pathologisch-anatomischen Veränderungen des Myokards und der Herzganglien beim Scharlach, Jahrb. f. Kinderh. **30**:491, 1914.

29. Brody, H., and Smith, L. W.: The Visceral Pathology in Scarlet Fever and Related Streptococcus Infections, Am. J. Path. **12**:373, 1936.

believed to occur. They found the myocardium involved in over 90 per cent of 44 hearts of patients dying from scarlet fever and in 15 hearts of patients with possible scarlet fever. This is in contrast to the statement by Gardère [30] that myocarditis is rarely encountered in scarlet fever and rarely diagnosed clinically. In view of Brody and Smith's findings, it is perhaps possible that more careful clinical analyses of signs and symptoms referable to heart disease in scarlet fever may disclose facts from which a clinical diagnosis of myocarditis in general may be made in the future.

Other Contagious Diseases.—Judging from the lack of available literature, myocarditis in other contagious diseases in children, such as smallpox and varicella, seems to be exceedingly rare. However, one must take into consideration that there probably are no studies available with detailed microscopic examinations of the heart. Such studies are needed to prove whether or not the concept of the rarity of myocarditis in these diseases is correct.

Epidemic Meningitis.—Myocarditis occasionally occurs in epidemic meningitis. It may or may not be associated with endocarditis. Hartwell [31] described endocarditis and myocarditis in a 13 year old boy. One of us [32] previously reported 2 instances of meningococcic myocarditis not associated with endocarditis. The patients were 19 and 22 years old respectively. Both at autopsy were seen to have fibrinopurulent meningococcic meningitis. It was pointed out at the time that associated myocarditis, with resulting myocardial failure, seriously influences the prognosis in meningococcic meningitis, not only because of myocardial failure but because myocarditis is seemingly the result of an overwhelming infection with meningococci.

In our 97 instances of myocarditis in children, there were 4 in which the condition was associated with meningitis. In 2 boys, 9 months and 12 years of age, with meningitis caused by Haemophilus influenzae, the myocardium showed involvement of both the interstitial tissue and the parenchyma. Most of the inflammatory exudate consisted of endothelial leukocytes with only a few polymorphonuclear leukocytes. In 1 of these hearts acute fibrinous pericarditis was also encountered. In a 1 year old boy with meningitis caused by streptococci most of the inflammatory cells in the myocardium were polymorphonuclear leukocytes. A 6 month old boy with meningitis caused by pneumococci, the only child among the 4 who died suddenly, had diffuse myocarditis. It must be pointed out, however, that a culture of blood taken at the time of the postmortem examination remained sterile. Of Vischer's [7] 27 patients with myocarditis there was 1 who had diffuse leptomeningitis.

Albert,[17] who examined the hearts of 13 children who died of meningitis, found myocarditis in only 1. The inflammatory exudate consisted of lymphocytes and polymorphonuclear leukocytes.

Poliomyelitis.—As was reported previously,[33] in patients with poliomyelitis we found the myocardium involved in 6 of 7 hearts examined. Five of the 6 patients were children. Since that communication was published, we have encountered 2 more instances of myocarditis in poliomyelitis. Because of the rarity of this finding, the clinical data for these children will be given more fully.

A white boy 16 years old entered the hospital with bulbar poliomyelitis of two days' duration. Physical examination on his admission revealed an acutely ill youth, with a temperature of 101 F., a pulse rate of 96, a respiratory rate of 20 and an arterial blood pressure of 110 systolic and 85 diastolic. His speech was thick and slurred. There was severe rigidity of the neck, and the Kernig and Brudzinski signs were positive. The heart and lungs were normal on examination. The patient's course was progressively downward. His speech became more nasal; the uvula deviated up and to the right; the left upper abdominal and cremasteric reflexes disappeared, and some difficulty in swallowing developed. The temperature rose to 103 F. The respiratory rate was 12 to 16 and the pulse rate 80 to 90. Forty-eight hours after admission the patient had sudden left ventricular failure, with a pulse rate of 180, a respiratory rate of 64 and severe pulmonary edema. In spite of supportive measures he died twelve hours later.

A white girl 10 years old had had poliomyelitis for one month before entering the hospital. She was transferred from a hospital for contagious diseases, where she had been in a respirator until eight days prior to discharge. Physical examination on admission revealed complete paralysis of the right arm and leg. Respiration was diaphragmatic. The intercostal muscles were

30. Gardère, C.: Myocardite scarletineuse, Médecine **20**:646, 1939.

31. Hartwell, R. M.: Meningococcic Endocarditis and Myocarditis, Am. J. Dis. Child. **58**:823 (Oct.) 1939.

32. Saphir, O.: Meningococcic Myocarditis, Am. J. Path. **12**:677, 1936.

33. Saphir, O., and Wile, S.: Myocarditis in Poliomyelitis, Am. J. M. Sc. **203**:781, 1942.

paralyzed. The temperature was 100 F., the pulse rate 108, and the respiratory rate 30. Kenny treatment was started, and for a period of almost two and one-half months the child did well, showing a slow but steady improvement. Ten weeks after admission she complained of a sore throat, cough and abdominal pain. The temperature rose to 101 F. The urine showed many erythrocytes and leukocytes. The arterial blood pressure was 130 systolic and 80 diastolic. The following day the patient's condition was worse. The temperature was 99.6 F. The pulse rate, however, had risen to 144. Crackling rales were heard at the bases of both lungs. The heart was enlarged to the left, and the tones were distant. The electrocardiogram revealed supraventricular tachycardia with right ventricular strain. The patient was given sulfonamide compounds and dextrose intravenously and digifolin, atropine and oxygen. Her condition became progressively worse; the arterial blood pressure dropped to 106 systolic and 70 diastolic, and she died.

Microscopically, the myocarditis present in our patients with poliomyelitis was primarily interstitial, with perivascular foci of lymphocytes and neutrophils at times predominating. The involvement in some sections was only minimal, but in others it was much more extensive. Three of 6 sudden deaths of patients with poliomyelitis previously reported [33] could be attributed to myocarditis. The relationship of bronchopneumonia, so often present in children with poliomyelitis, to myocarditis was discussed in the same report, and the conclusion was reached that pneumonia did not seem the likely source of the myocardial infection.

Recently Dublin and Larson [34] studied the pathologic changes in 12 instances of poliomyelitis. Acute myocarditis was found in 2, in the absence of any of the usual sources of such infections. Peale and Lucchesi [35] found myocarditis of some degree, in addition to toxic and degenerative changes, in 7 of 9 hearts of patients with poliomyelitis. Of these 7 patients 5 were children, 1 of whom had typical rheumatic myocarditis. These authors stressed that the clinical signs of cyanosis and rapid, thready pulse in poliomyelitis are suggestive of myocarditis, although none of their patients died of myocardial failure and in no instance was myocarditis suspected clinically.

Pneumonia.—(*A*) Bronchopneumonia: There were 12 children with bronchopneumonia and myocarditis. Of these the clinical records of only 5 were available. Three of these 5 children died of heart failure. One of the three had empyema, pericarditis and otitis media. In none was there a clinical diagnosis of myocarditis. Microscopically the myocarditis was more or less diffuse. Mainly polymorphonuclear leukocytes were encountered. There were no abscesses. In 4 instances of bronchopneumonia Albert [17] found no histologic change in the myocardium. Stone [36] stated that of 37 hearts from patients who died of bronchopneumonia, interstitial myocarditis was present in 2.7 per cent.

(*B*) Lobar Pneumonia: There were 3 children with lobar pneumonia and myocarditis. In all 3 instances the myocarditis was predominantly interstitial. Monocytes and polymorphonuclear leukocytes were found in about equal proportions. Judging from the available records, the course of the disease did not differ from that of pneumonia not complicated by myocarditis. The pulse rate, however, in 2 of these 3 children was distinctly higher than would ordinarily be expected in uncomplicated pneumonia. An 8 year old girl had a pulse rate of 120 to 160 per minute, with a temperature of 99 to 103 F. A 2½ year old girl had a pulse rate of 132 to 148 per minute, with a temperature of 99 to 101 F. The record of the pulse rate of the third child was not available.

Pyemia.—Sixteen instances of pyemia with abscesses in the myocardium were encountered. The most common cause of pyemia was cellulitis, which was present in 5 instances. In 2 children the pyemia resulted from retropharyngeal abscesses. Among 14 myocardial abscesses due to miscellaneous infection, Flaxman [37] found 4 in children. The clinical diagnoses were cellulitis, septicemia, poliomyelitis and otitis media respectively. However, at autopsy bacterial endocarditis and acute osteomyelitis were found to be the main underlying diseases. Five of 7 additional myocardial abscesses associated with acute osteomyelitis found by Flaxman were in children. Among our children were 2 with osteomyelitis. In 10 hearts acute endocarditis was evident. However, because of the fact that evidence of pyemia (abscesses in other organs) which was definitely older than the endocarditis was also seen in these patients at autopsy, the condition of the heart was classified as pyemia

34. Dublin, W. B., and Larson, C. P.: Pathologic Findings in Poliomyelitis, Am. J. Clin. Path. **13**:15, 1943.

35. Peale, A. R., and Lucchesi, P. F.: Cardiac Muscle in Poliomyelitis, Am. J. Dis. Child. **65**:733 (May) 1943.

36. Stone, W. J.: The Heart Muscle Changes in Pneumonia, with Remarks on Digitalis Therapy, Am. J. M. Sc. **163**:659, 1922.

37. Flaxman, N.: Myocardial Abscess, J. A. M. A. **122**:804 (July 17) 1943.

rather than as bacterial endocarditis. For only 1 of the 16 children with pyemia was a diagnosis of myocarditis made. Lawrence and Scott [38] reported the sudden death of an adult as the result of myocardial abscess. One of our patients died suddenly, and in 2 others the clinical course of the disease was rapid and stormy, culminating in unexpected, though not sudden, death. The roentgenograms of these 2 children disclosed a globular heart, and shortly before the death of the patient edema of the ankles developed. Routine clinical examination of the other children in this group disclosed no evidence to suggest possible myocardial failure. Flaxman [37] stated recently that among 14,160 autopsies, myocardial abscesses were noted in 29. This, offhand, seems an insignificant number (0.2 per cent). However, one must take into consideration that the abscesses are often extremely small and that a number of sections of the myocardium must be cut and examined to rule out or substantiate the presence of abscesses. In routine examinations usually only a few sections are cut from the myocardium, and at times the diagnosis of cardiac lesions is based on gross examination alone. Thus, statistical reports on the presence of abscesses in the myocardium taken from routine autopsy records do not give a true incidence.

ISOLATED MYOCARDITIS

There were 3 instances of isolated myocarditis in this series. The children were 15 months, 3 years and 10 years old, respectively. Two were boys, and 1 was a girl. The youngest, a white boy, had a weight at birth of 9 pounds (4,100 Gm.). The delivery was normal, and he was breast fed for three months. The mother had noted slight cyanosis for some time prior to the infant's sudden death. There was no history of any previous infectious disease. The child was not hospitalized but died at home. The autopsy disclosed acute myocarditis. Neither the endocardium nor the pericardium was involved. The second child was a 3 year old white girl with a clinical diagnosis of cirrhosis of the liver. There were ascites and edema of the legs and ankles. No other conditions pertinent to myocardial involvement were noted. The child died rather unexpectedly. The autopsy disclosed early periportal cirrhosis. The heart was enlarged, and microscopically subacute myocarditis was seen. Again neither the pericardium nor the endocardium was involved. The third child was a 10 year old Negro boy. As far as could be ascertained, he had been in good health but died suddenly. Because of the sudden unexplained death and because the patient had been in contact with children in whom scarlet fever had developed, the department of health requested an autopsy. Grossly, nothing was found but an enlarged and dilated heart. Neither the endocardium nor the pericardium showed any abnormality. Histologically, there was acute and subacute myocarditis. No pathologic changes were encountered elsewhere.

These 3 patients are most interesting. Two of the children had no history of a preceding or concurrent disease which might account for the myocarditis, nor was anything noted at autopsy to which the cause of myocarditis could be ascribed. The other child showed only periportal cirrhosis, which, as far as we were able to judge, was not related to the myocarditis. Thus, these 3 instances are examples of "myocarditis of unknown origin unaccompanied by endo- or pericarditis, and which occurs in patients who have no other disease which may be correlated with the myocarditis. Such myocarditis may be present in apparently healthy individuals who, more or less suddenly, develop progressive myocardial weakness and succumb quickly. This type of myocarditis has been described under the name of isolated myocarditis, Fiedler's myocarditis, idiopathic myocarditis, etc." [39]

The literature on this subject has been summarized recently elsewhere.[40] According to Vischer,[7] the first report of a child with isolated myocarditis was made by Förster,[41] Fiedler's former assistant, in 1906. As early as 1901, however, Zuppinger [42] reported such a condition in a 3 year old child. Since 1929, when attention was again called to this disease, a number of cases have been reported. Most of the patients have been adults. There are, however, a number of instances in which this disease occurred in infants and children. It may be of interest to point out that, apparently because of the sudden and unexpected death of some of these patients and because of the belief that sudden death often occurs in status thymicolymphaticus, this type of myocarditis and status thymicolymphaticus have been linked by several authors. Thus, Ceelen [43]

38. Lawrence, F. F., and Scott, E.: Myocardial Abscess with Chronic Myocarditis, Ohio State M. J. **25**:209, 1929.

39. Scott, R. W., and Saphir, O.: Acute Isolated Myocarditis, Am. Heart J. **5**:129, 1929.

40. Saphir, O.: Isolated Myocarditis, Am. Heart J. **24**:167, 1942.

41. Förster, F.: Ueber Myokarditis und Gefässerkrankungen im Kindesalter insbesonders nach akuten Infektionskrankheiten: Akute primäre Myokarditis, Myokarditis nach Verbrennungen, bei Erkrankungen der Haut und bei Diphtherie, Deutsches Arch. f. klin. Med. **85**:35, 1906.

42. Zuppinger: Ueber Herztod bei anscheinend bedeutungslosen Oberflächl: Geschwuersprozessen, Wien. klin. Wchnschr. **34**:799, 1901.

43. Ceelen, W.: Status thymico-lymphaticus, Berl. klin. Wchnschr. **53**:755, 1916.

and also Riesenfeld [44] expressed the opinion that the cellular infiltrations in the myocardium in these instances are specific for status thymicolymphaticus and might explain the sudden death. Ceelen [43] (1916) reported 5 cases of myocarditis with status thymicolymphaticus. In all of these cases the myocarditis was recognized only on microscopic examination. Löwenthal [45] (1920) referred to the unusual localization of lymphocytes in the myocardium in status thymicolymphaticus. He reported on a 16 month old boy with cyanosis, cough, diarrhea and vomiting. Because of the obviously erroneous conception of Ceelen and others who regarded this type of myocarditis as part of the picture of status thymicolymphaticus, many instances of such a combination are not recorded in the literature as examples of isolated myocarditis. Apparently, however, they should be classified as such. Thus the number of cases of isolated myocarditis in children is definitely higher than one would be led to believe from the current literature.

Fahr and Kuhle [46] found no changes in the myocardium in 3 of 6 instances of status thymicolymphaticus, while in the other 3 more or less pronounced changes were revealed grossly and microscopically. Rieder,[47] one year later, published observations on 9 children, 6 months to 6 years old, with status thymicolymphaticus. Six of these children died suddenly. Seven of the 9 had within the myocardium infiltrations not only of small round cells but of plasma cells, eosinophilic cells and neutrophilic leukocytes. Rieder did not think that these cellular infiltrations were associated with the status thymicolymphaticus. Blühdorn,[48] two years later, expressed the belief that myocarditis observed by him in a child 1½ years old was due not alone to status thymicolymphaticus but to an eczematous lesion. Bernheim-Karrer [49] as early as 1905 drew attention to a probable case of isolated myocarditis (the patient was an 18 month old boy with no fever but with a pulse rate of 220 per minute and sick for only two days), and in 1923 [50] he expressed much doubt as to any relationship between myocarditis and status thymicolymphaticus. At that time he also briefly mentioned myocarditis in 2 children with eczema and discussed more fully the conditions observed in a boy 13½ months old who had eczema on the cheeks, head and thorax. Fourteen days after the child was first seen by Bernheim-Karrer, he suddenly died. Autopsy revealed diffuse myocarditis. The possibility that the myocarditis had been caused by a blood-borne infection was suggested, the portal of entry being the eczematous lesion. Such instances of association of myocarditis with eczema apparently form the basis of the opinion that allergy might explain some myocardial changes.

Vischer [7] (1924) found 5 instances of primary acute interstitial myocarditis in children. He definitely stated that myocarditis and status thymicolymphaticus could in no way be correlated, that each was a distinct entity. Steiner and Bogin [51] (1930) found, microscopically, edema and hydropic degeneration in the myocardium, but no infiltration of round cells, in a 3 month old boy with idiopathic cardiac enlargement associated with status thymicolymphaticus. Singer [52] reported the sudden death of 2 infants, 6 months and 13 months old, and suggested that a clinically overlooked infection, possibly diphtheria, might have caused the myocarditis which, however, histologically was obviously isolated myocarditis. Maslow and Lederer [53] in studying a 21 month old child who died suddenly found predominantly interstitial myocarditis and thought that it might have been caused by toxemia. In Smith and Stephen's series,[54] there were 2 infants with isolated myocarditis. Taussig and Oppenheimer [55] reported a 6 month old child with myocarditis. Because of the fact that the myocarditis was granulomatous in type, the question was raised as to a tuberculous or syphilitic origin. There were tuberculous nodes in the

44. Riesenfeld, A.: Ueber primäre Herzhypertrophie im frühen Kindesalter und ihre Beziehung zum Status Thymicolymphaticus, Jahrb. f. Kinderh. **86**:419, 1917.

45. Löwenthal, K.: Der sogenannte Status thymicolymphaticus als selbstständige Krankheit, Jahrb. f. Kinderh. **93**:1, 1920.

46. Fahr, T., and Kuhle, J.: Zur Frage des Kropfherzens und der Herzveränderungen bei Status thymicolymphaticus, Virchows Arch. f. path. Anat. **233**:286, 1921.

47. Rieder, H.: Ueber Rundzellen Infiltrate im Myokard bei Status thymicolymphaticus, Jahrb. f. Kinderh. **97**:9, 1922.

48. Blühdorn, K.: Zur Klinik der primären Herzdilatation im frühen Kindesalter (Myocarditis Interstitialis), Monatschr. f. Kinderh. **29**:193, 1924.

49. Bernheim-Karrer, I.: Beitrag zur Kenntnis der Ekzem Todesfälle, Jahrb. f. Kinderh. **62**:767, 1905.

50. Bernheim-Karrer, I.: Ekzemtod und Myokarditis, Ztschr. f. Kinderh. **35**:120, 1923.

51. Steiner, M., and Bogin, M.: Idiopathic Cardiac Enlargement Associated with Status Thymicolymphaticus, Am. J. Dis. Child. **39**:1255 (June) 1930.

52. Singer, L.: Ueber akute Herztodesfälle im frühesten Kindesalter, Ztschr. f. Kinderh. **53**:660, 1932.

53. Maslow, H. L., and Lederer, M.: Interstitial Myocarditis in a Child Nineteen Months of Age, Am. J. Dis. Child. **45**:807 (April) 1933.

54. Smith, F. M., and Stephens, R. L.: Acute, Subacute and Chronic Interstitial Myocarditis: Six Cases, Tr. A. Am. Physicians **53**:120, 1938.

55. Taussig, H. B., and Oppenheimer, S. H.: Severe Myocarditis of Unknown Etiology, Bull. Johns Hopkins Hosp. **59**:155, 1936.

mediastinum, and the patient had contracted syphilis after a blood transfusion. In a previous communication [40] it was pointed out that isolated myocarditis may be subdivided into a granulomatous and a more or less diffuse form. In Taussig and Oppenheimer's case the myocarditis was granulomatous.

Lindberg [56] reported the sudden death of an 11 month old boy who had a history of having had whooping cough five months before. (The patient also showed evidence of rickets.) Lindberg pointed out that the myocarditis was initially of the so-called serous type and that this later resulted in fibrosis. This inflammation is similar to the one described by Rössle [57] and later by Eppinger, Kaunitz and Popper.[58] This condition resembles the type of myocarditis seen in beriberi, as described by Wenckebach.[59] Recently Smith and Furth [60] suggested that fibrosis of the endocardium and myocardium and that isolated myocarditis may be the result of a deficient diet and could represent a variant of beriberi heart.

Kenny and Sanes [61] described 2 infants with hypertrophy and dilatation of the heart and parenchymatous myocarditis. Though they do not classify the myocardial changes as isolated myocarditis, from their description it seems that they should be classified as such. In our experience hypertrophy and dilatation are commonly observed in isolated myocarditis, and this relationship was also stressed as early as 1914 by Oberndorfer.[25] One of Kenny and Sanes's patients was a white girl, 1 year old, who had an infection of the respiratory tract for three weeks. After a two week interval in which the patient had good health, cough and anorexia appeared. The temperature was 100 F. (rectal) and the pulse rate 140 per minute. The heart was enlarged, and a systolic murmur was present. Pericarditis was considered as a clinical diagnosis. (It should be mentioned that not infrequently a clinical diagnosis of "pericarditis" is made for patients with isolated myocarditis.) At autopsy severe dilatation and slight hypertrophy of the heart and lobular pneumonia in the upper lobe of the left lung were observed. The valvular apparatus was intact. Microscopically, the endocardium was slightly thickened. The muscle fibers were the seat of degenerative changes of various degrees, and slight interstitial edema was noted. There were focal infiltrations of round cells beneath the epicardium and around the vessels. No bacteria could be demonstrated. The second patient was a 6 month old white boy admitted to the hospital because of dyspnea and cyanosis of five weeks' duration. On physical examination the heart was enlarged, the cardiac rate was rapid and the cardiac sounds of fair quality. No murmurs were heard. The child died three hours after admission to the hospital. At autopsy severe dilatation and moderate hypertrophy of the heart were noted. The endocardium showed slight fibrosis. The valvular apparatus was intact. Microscopically, there were myocardial fibrosis and slight interstitial edema, with degenerative changes of the musculature. Focal cellular infiltrations, especially of leukocytes, were noted. There were no bacteria. Though the changes in the myocardium somewhat resembled those seen in diphtheria, the authors emphasized that there was no conclusive evidence that a diphtheritic infection had been present in either patient. Neither did they believe that the condition could be classed as so-called idiopathic enlargement of the heart, as described by Stoloff,[14] Steiner and Bogin [51] and others. Though not mentioned, it also seems clear that these patients did not have glycogenosis (von Gierke's disease). Thus the disorder must be classified as isolated myocarditis.

Fox and Overstreet [62] reported the case of a 3 year old boy who after an infection of the upper respiratory tract had poor appetite and was listless. There was a slight cough, and later slight cyanosis developed. The heart was enlarged, and a murmur was heard at some examinations but not at others. Electrocardiographic records were apparently normal. The pulse rate varied between 80 and 130. The temperature was normal or subnormal. Fibrillation and showers of extrasystoles occurred at times. Cultures of the blood remained sterile. Before death cyanosis became much more severe and

56. Lindberg, K.: Problem of So-Called Isolated Chronic Myocarditis, Acta med. Scandinav. **95**:281, 1938.

57. Rössle, R.: Ueber wenig beachtete Formen der Entzündung von Parenchymen und ihre Beziehung zur Organsklerosen, Verhandl. d. deutsch. path. Gesellsch. **27**:152, 1934.

58. Eppinger, H.; Kaunitz, H., and Popper, H.: Die seröse Entzündung: Eine Permeabilitäts-Pathologie, Berlin, Julius Springer, 1935.

59. Wenckebach, K. F.: Das Beriberi-Herz, in Aschoff, L.; Elias, H.; Eppinger, H.; Sternberg, C., and Wenckebach, K. R.: Pathologie und Klinik in Einzeldarstellungen, Berlin, Julius Springer, 1934, vol. 6.

60. Smith, J. J., and Furth, J.: Fibrosis of the Endocardium and the Myocardium with Mural Thrombosis: Notes on Its Relation to Isolated (Fiedler's) Myocarditis and to Beriberi Heart, Arch. Int. Med. **71**:602 (May) 1943.

61. Kenny, F. E., and Sanes, S.: Dilatation and Hypertrophy of the Heart in Infancy Due to Parenchymatous Myocarditis, J. Pediat. **3**:321, 1933.

62. Fox, I. R., and Overstreet, R. M.: Isolated Myocarditis: Report of Case, Northwest Med. **40**:89, 1941.

peripheral edema appeared. At autopsy it was noted that the heart was dilated and the myocardium thinned. Mural thrombi were present. Microscopically, areas of dense fibrosis and small scattered collections of lymphocytes were found throughout the myocardium.

A more recent report by Greenebaum, Felson and Zeligs [63] described a 1 year old white girl with a history of rapid breathing, grunting respiration, irritability and drowsiness. The temperature was 99 F. (rectal), and the pulse rate was 160 beats per minute. A systolic murmur was present, heard best over the mitral area. The electrocardiogram showed sinus tachycardia and changes in the T wave. During the child's stay at the hospital the pulse rate remained rapid and was never below 130 per minute. Gradually cyanosis developed, and the child died with terminal bronchopneumonia. At autopsy the heart was seen to be enlarged. The valves appeared normal, and the myocardium showed grossly no abnormal changes except edema. Microscopically, in addition to degenerative changes, there were focal subacute myocarditis and perivascular fibrosis. The inflammatory cells were chiefly plasma cells, lymphocytes and large mononuclear leukocytes.

These reports are interesting in that they definitely show how difficult it is to diagnose isolated myocarditis clinically; even at autopsy the diagnosis often cannot be made on gross examination. The clinical picture is one of progressive myocardial failure unassociated with the usual causes of myocardial damage. The outstanding symptoms are tachycardia out of all proportion to the temperature of the patient, frequently cardiac enlargement and often increasing cyanosis. The electrocardiogram may reveal changes in the T wave. The course of the disease ordinarily is rapid and progressively downhill. Death may occur suddenly and unexpectedly. Isolated myocarditis should be suspected in infants and children with persistent tachycardia for which no other cause can be found. These reports also show the importance of careful microscopic study. Most of these myocarditides were diagnosed from the histologic sections in which the changes were so severe that it was difficult to reconcile them with the fact that, grossly, the myocardium showed little deviation from the normal.

The cause of isolated myocarditis is not known. Rheumatic fever or other infectious diseases or toxemias as possible causative factors can be ruled out. Lately there has been some discussion as to the possible allergic nature of isolated myocarditis and as to whether or not myocarditis may be the result of an idiosyncrasy to certain chemicals (for instance, arsene, sparteine and epinephrine). Instances in which myocarditis developed in children with eczema may have suggested such a causation. Recently it has been found that the sulfonamide drugs may cause myocarditis.[64] However, this form of myocarditis is probably different from isolated myocarditis, which was described so often prior to the era of therapy with these compounds. Vitamin deficiencies, as previously mentioned, have also been suggested as a possible cause.

63. Greenebaum, G. V.; Felson, W., and Zeligs, M.: Acute Interstitial Myocarditis in an Infant, J. Pediat. **18**:799, 1941.

MYOCARDITIS ASSOCIATED WITH ENDOCARDITIS

Bacterial Endocarditis.—In our series there were 5 patients with myocarditis associated with bacterial endocarditis. In all of them acute vegetative and ulcerative endocarditis was found, which involved the mitral valve alone in 2 instances, the mitral and aortic valves in 1, the tricuspid valve only in 1 and the tricuspid and pulmonic valves in 1. Hemolytic streptococci were recovered from the circulating blood of 3 patients and staphylococci from the blood of 1. One child died suddenly soon after admission to the hospital, and no blood was taken for cultures. The cause of the endocarditis was found to be purulent arthritis, suppurating lymphadenitis with thrombosis of the internal jugular vein and, in 2 patients, mastoiditis. In 1 child the portal of entry could not be determined at autopsy. This child, who had died suddenly, showed, clinically, severe cyanosis. His temperature was 98.6 F., and his pulse rate was 96 per minute. The other children had temperatures and pulse rates respectively of 100 F. with 120 to 140 pulse beats per minute, 101 to 105 F. with 120 to 150 beats per minute and 101 to 102 F. with 100 to 120 beats per minute. Histologically, the myocarditis was characterized mainly by a diffuse infiltration of polymorphonuclear leukocytes, noted principally in the interstitial tissue but also destroying cardiac muscle fibers. No abscesses were encountered. (Abscesses in the myocardium have already been discussed, in the section on pyemia.) Occasionally, minute infarcts were seen, similar to those to be discussed in connection with subacute bacterial endocarditis. Libman [65] pointed out over twenty years ago that lesions in the heart in acute

64. French, A. J., and Weller, C. V.: Interstitial Myocarditis Following the Clinical and Experimental Use of Sulfonamide Drugs, Am. J. Path. **18**:109, 1942.

65. Libman, E.: Characteristics of Various Forms of Endocarditis, J. A. M. A. **80**:813 (March 24) 1923.

bacterial endocarditis consist in the main of infiltrations of polymorphonuclear leukocytes. In none of the 5 instances of myocarditis associated with bacterial endocarditis was a clinical diagnosis of myocarditis made. Endocarditis was diagnosed twice and septicemia 3 times. Though it is not specifically stressed in the literature, the prevalent opinion seems to be that myocardial inflammatory changes are often encountered in acute bacterial endocarditis. Flaxman [37] found myocardial abscesses twice in children with bacterial endocarditis.

Subacute Bacterial Endocarditis (Endocarditis Lenta).—Included in this series were 7 children with subacute bacterial endocarditis, 5 of whom gave a definite history of rheumatic fever. Cultures of blood of 4 of the 7 yielded Streptococcus viridans. Three of the children died of clinically recognized heart failure, and 2 died of emboli in one of the cerebral arteries. In 3 children the electrocardiogram disclosed myocardial involvement, and in 1 it revealed right ventricular preponderance and sinus tachycardia. In all of the children, with the exception of 1 who was brought to the hospital in a moribund condition, the pulse rate was higher than would have been expected from the temperature.

Autopsy disclosed subacute bacterial endocarditis in all of these children. The aortic and mitral valves were involved in 4 hearts, with the tricuspid also in 2; however, the endocarditis in the tricuspid valve was healed. The mitral valve alone was involved 3 times. The vegetations were engrafted on a valve which obviously was the seat of an old (healed) endocarditis. The mural endocardium was involved in all instances. The myocardium, grossly, was pale gray and of parboiled appearance. Myocarditis became evident only on histologic examination. It was characterized by diffuse infiltration of lymphocytes and a few polymorphonuclear leukocytes, particularly pronounced in the interstitial tissue but also involving the cardiac muscle fibers. In addition, focal areas of round cell infiltration were found surrounding small blood vessels. Six of the 7 hearts also had Aschoff bodies in the myocardium. Minute infarcts, mainly in the state of organization, were found in every instance. The observations in this series were comparable with the results of a previous study of 10 instances of subacute bacterial endocarditis.[66] In the present series a clinical history of rheumatic fever was obtained for 6 of the 7 children. The relation between rheumatic infection and subacute bacterial endocarditis has been previously investigated.[67] Although allergy seems an attractive explanation of rheumatic fever and its relation to subacute bacterial endocarditis, evidence was brought forward which spoke against the assumption that rheumatic fever and subacute bacterial endocarditis are manifestations of the same disease, differing only in the immunologic response of the host. It was also thought that the weight of evidence indicated that the only relationship between rheumatic fever and subacute bacterial endocarditis is that the injury due to a previous rheumatic infection predisposes the valve to a subsequent subacute bacterial endocarditis. Since the scope of this paper does not warrant a discussion of the relationship between rheumatic fever and subacute bacterial endocarditis, we merely wish to stress that the present study indicates that the myocardium is involved in subacute bacterial endocarditis, apparently just as it is in rheumatic endocarditis. As previously pointed out, because the time interval between the original rheumatic infection and the subsequent bacterial endocarditis is not as long in children as in adults, if enough sections are cut from the myocardium, Aschoff bodies may be found in a higher percentage in the hearts of children than in those of adults with subacute bacterial endocarditis.

As already stated, 3 of the 7 children with subacute bacterial endocarditis showed clinical evidence of heart failure. Absence of heart failure, however, is often regarded as one of the important negative features of subacute bacterial endocarditis. Thayer [68] stressed that the terminal features of infective endocarditis are generally those of grave septicemia. The relation of subacute bacterial endocarditis, heart failure and myocardial damage was investigated by Buchbinder and Saphir [69] in a study involving 40 patients. Clinically, evidence of heart failure of fairly advanced degree was encountered in 18 patients (45 per cent). At necropsy, in many instances chronic passive hyperemia of different degrees was noted. Lewis [70] also was apparently impressed with the evidence of cardiac failure as a cause of death of patients with bacterial endocarditis. He stated that cardiac failure with congestion is rarely present in the early stages of

66. Saphir, O.: Myocardial Lesions in Subacute Bacterial Endocarditis, Am. J. Path. **11**:143, 1935.

67. Saphir, O., and Wile, S.: Rheumatic Manifestations in Subacute Bacterial Endocarditis in Children, Am. Heart J. **9**:29, 1933.

68. Thayer, W. S.: Observations on Rheumatic Pancarditis and Infective Endocarditis, Ann. Int. Med. **5**:247, 1931.

69. Buchbinder, W. C., and Saphir, O.: Heart Failure in Subacute Bacterial Endocarditis, Arch. Int. Med. **64**:336 (Aug.) 1939.

70. Lewis, T.: Diseases of the Heart, ed. 2, New York, The Macmillan Company, 1937.

subacute bacterial endocarditis but is so frequent in the later stages as to be one of the chief causes of death.

In regard to anatomic changes in the myocardium in subacute bacterial endocarditis there are only a few references available in the literature. The myocardial changes may be summarized as consisting of cloudy swelling, fatty degeneration, petechial hemorrhages, acute myocarditis, foci of necrosis, abscesses, areas of perivascular acute and chronic (nonspecific) inflammation, emboli in branches of the coronary arteries, minute infarcts, Aschoff bodies and perivascular fibrosis. Minute infarcts, most commonly in the organizing state, not only are frequently found but constitute, in our opinion, the most characteristic myocardial change. They are brought about by minute emboli arising from the vegetation of the aortic valve. Often a number of sections must be examined before the emboli can be demonstrated.

Frequently one finds mentioned in the literature that Bracht-Wächter bodies are the significant lesions in the myocardium of hearts with subacute bacterial endocarditis. In a previous study [66] the Bracht-Wächter bodies were discussed and the conclusion was reached that from the literature it is extremely uncertain just what constitutes a Bracht-Wächter body and that various observers have described different lesions. It was recommended, therefore, that the term be discarded.

Myocardial inflammatory lesions in subacute bacterial endocarditis not infrequently occur as the result of a direct extension of mural endocardial lesions into the myocardium. Sometimes so-called mycotic ulcerations may result (Kidd [71]). In none of the 7 hearts examined did the mural endocarditis extend into the myocardium.

"Rheumatic Type" of Myocarditis.—Under this heading are considered changes in the myocardium of hearts with recent and old endocarditis possibly but not definitely of rheumatic origin. These changes are not characteristic enough to warrant a diagnosis of rheumatic myocarditis.

There were 13 children with changes of this type. The clinical records of only 10 of them were available. Eight of the 10 showed clinical evidence of heart failure, and a clinical diagnosis of myocarditis (rheumatic myocarditis) was made for 3. The electrocardiograms showed myocardial involvement in these 3 instances. In 5 of the 10 there was an appreciable discrepancy between the pulse rate and the temperature.

The myocardial changes were characterized principally by perivascular fibrosis with perivascular infiltrations of lymphocytes. Often there was diffuse fibrosis of the myocardium, involving principally the interstitial tissue, and various numbers of lymphocytes and endothelial cells were scattered throughout. As mentioned before, in not a single instance were Aschoff bodies encountered, though acute endocarditis was observed in the hearts of 7 of 13 children, with acute pericarditis in addition in 2. Histologically, in these 7 instances minute foci of necrosis and infiltrations of polymorphonuclear leukocytes, lymphocytes and histiocytes were found in the myocardium in addition to some edema. The lesions were similar to those described by Skworzoff.[72]

SPECIFIC MYOCARDITIS

Rheumatic Myocarditis.—Myocarditis in, and as the result of, acute rheumatic fever is practically the only type of myocarditis in children which has received much attention from both the clinician and the pathologist. Since its association with rheumatic infection is known, electrocardiographic records of patients with rheumatic heart disease are taken, and myocarditis is diagnosed clinically by physicians who are aware of its frequent existence. The myocarditis is often anatomically so diffuse, so extensive and, because of the Aschoff bodies, so characteristic that there are at the present time only a few instances of acute or chronic rheumatic endocarditis on record which do not also bear the label "myocarditis." Because of the severe involvement of the myocardium, Gibson [73] stated that the cardiac musculature rarely fails during childhood because of the additional burden placed on it by valvular lesions or pericardial adhesions; it fails because it is suffering from active invasion by the rheumatic virus.

As stated previously, in this study only those conditions were designated as rheumatic myocarditis which were undoubtedly of rheumatic origin as determined by the finding of definite Aschoff bodies in the myocardium. In differentiating Aschoff bodies the strictest criteria were used, as outlined in a previous publication. If inflammatory changes were found in the myocardium which only resembled Aschoff bodies

71. Kidd, J. G.: Instant Death in Bacterial Endocarditis: Report of a Case with Mycotic Ulceration of the Conduction System, Ann. Int. Med. **9**:78, 1935.

72. Skworzoff, M. A.: Histomorphologie der rheumatischen Myokarditis und ihre klinische Bedeutung, Acta med. Scandinav. **96**:344, 1938.

73. Gibson, S.: Rheumatic Fever and Chorea, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1942, vol. 2.

or if such changes were encountered in hearts with endocarditides for which there was no definite proof of rheumatic origin the condition was classified with the "rheumatic type" of myocarditis. It is fully realized that by the use of such rigid criteria we may have failed to recognize some rheumatic lesions (Aschoff bodies) and thus failed to make the diagnosis of rheumatic myocarditis. We are certain, however, that every lesion classified as rheumatic myocarditis was a true example of that condition. Unquestionable rheumatic myocarditis, fulfilling these criteria, was found in 19 instances. Clinical records were available for only 15. A review of these clinical records revealed that in all 15 instances the patients showed clinical evidence of myocardial failure and died as a result of myocardial insufficiency. However, a diagnosis of myocarditis was actually noted on the clinical records of only 4. A vast majority of these patients showed a higher pulse rate than would have been expected from the normal or slightly elevated temperature. The electrocardiograms of 13 of the 15 patients showed definite changes. One child died suddenly.

From our present knowledge, it must be conceded that the Aschoff body is the typical and characteristic myocardial lesion in acute rheumatic fever (rheumatic myocarditis). Though there are instances on record in which such nodules have been described as accompanying scarlet fever, it seems evident that either the lesions were not true Aschoff bodies or the patient had postscarlatinal rheumatic fever. Such a coincidence is apparently not infrequent (Ravenna [74]).

In addition to Aschoff bodies, the myocardium of these 19 patients also had much perivascular fibrosis with infiltrations of lymphocytes and more diffuse infiltrations of lymphocytes and a few endothelial leukocytes in the interstitial tissue. In the myocardium of some more recent patients there was some edema in the interstitial tissue in addition to the inflammatory cells. It must be realized that it is not so much the Aschoff bodies which are responsible for the myocardial failure in these children as the diffuse involvement of the myocardium by a seemingly nonspecific inflammation. Whether this nonspecific inflammation is the result of the activity of the same etiologic agent that causes Aschoff bodies, but perhaps in a more attenuated form (similar to the gelatinous type of pneumonia in instances of tuberculous pneumonia), or the result of a secondary invasion by an entirely different causative agent, cannot be decided. It is interesting in this respect to quote Skworzoff,[72] who stated that in acute rheumatic fever an exudative inflammation in the myocardium occurs which is characterized by foci of inflammatory edema and by the presence of lymphocytes, histiocytes and neutrophilic leukocytes, in addition to minute foci of necrosis. He also emphasized that this type of myocarditis is seen most commonly in children.

Myocarditis in Tuberculosis.—Three types of tuberculous myocarditis are usually differentiated, nodular, miliary and infiltrative. The last should be diagnosed only if the histologic changes are undoubtedly characteristic of tuberculosis or if tubercle bacilli can be demonstrated either by inoculation of guinea pigs or by staining. Auerbach and Guggenheim [75] in 10,165 autopsies on tuberculous patients found the myocardium involved in 0.28 per cent. In 973 children the percentage of incidence was 3.9. The older literature also discloses that the greater percentage of myocardial miliary tubercles occur in children. The fact that miliary tubercles in the myocardium are found more often in children may be due to the relatively larger areas of myocardium examined histologically. However, Roberts and Lisa [76] recently found tuberculous myocarditis to be more frequent in adults than in children. They stated that among 100 patients with pulmonary tuberculosis myocardial lesions of various kinds occurred in 69, 6 of whom were below the age of 17 years. Yet tuberculous myocarditis was found in only 10 out of the 69 patients, and in 8 of these 10 it was associated with generalized miliary tuberculosis. Only 1 of the 6 patients below the age of 17 had tuberculous myocarditis. Roberts and Lisa also found acute interstitial myocarditis (nonspecific) in 50 patients; the myocarditis appeared to have some relationship to nontuberculous infections.

In the 97 children studied by us, myocarditis was associated with tuberculosis 4 times. Actual tubercles were found in 2 infants, 3 months and 6 months old respectively. Both had diffuse miliary tuberculosis, and one of them had tuberculous leptomeningitis. The clinical course of these children did not differ appreciably from that of patients with generalized miliary tuberculosis in which the myocardium was not involved. In 2 other children, 2 months and 6 years old respectively, who also had diffuse miliary tuberculosis, the inflammation in the

74. Ravenna, P.: A Review of Recent Italian Work on Rheumatism: I. Rheumatic Fever, Ann. Rheumat. Dis. **1**:167, 1939.

75. Auerbach, O., and Guggenheim, A.: Tuberculosis of the Myocardium, Quart. Bull., Sea View Hosp. **2**:264, 1937.

76. Roberts, J. E., and Lisa, J. R.: The Heart in Pulmonary Tuberculosis, Am. Rev. Tuberc. **47**:253, 1943.

myocardium was diffuse and nonspecific. The myocardium of the 2 month old infant disclosed a more interstitial type of inflammation with many lymphocytes and a few endothelial leukocytes infiltrating the connective tissue septums. In the 6 year old child the involvement of the myocardium was rather localized and consisted also of lymphocytes and endothelial leukocytes. There was some new formation of connective tissue. These lesions were found to be predominantly perivascular. Tubercle bacilli could not be demonstrated in these hearts. The clinical findings in these 2 infants did not differ appreciably from those in the 2 previously mentioned children or from those in children who had the same type of tuberculosis but no myocardial involvement. However, it must again be emphasized that no particular attention was paid clinically to possible myocardial involvement.

Albert [17] found in a few hearts an "insignificant" number of lymphocytes and in 1 other perivascular infiltrations of lymphocytes in addition to tubercles. Recently more attention has been paid to nonspecific myocarditis in tuberculosis, and, as a matter of fact, there are those who believe that sometimes such nonspecific inflammatory cells resemble those seen in Aschoff bodies (Masugi and his co-workers [77]). Roberts and Lisa [76] recently discussed the relationship of these nonspecific inflammatory lesions to the lesions seen in rheumatic fever. It must be realized first that it is always possible to encounter tubercles and Aschoff bodies in the same heart, and, second, that simply because a lesion resembles an Aschoff body morphologically there is no proof that the lesion in question signifies rheumatic fever. However, apparently because of this resemblance and because of the finding of tubercles and Aschoff bodies in the same heart, Masugi and his associates [77] suggested that rheumatic fever might be tuberculous. This reminds one of the findings of Auersbach, Löwenstein and Löwenstein [78] who described the presence of tubercle bacilli in tonsillar tissues in recurrent rheumatic arthritis. It seems probable that these authors were dealing with patients who had both diseases.

It has also been suggested that the morphologically nonspecific inflammation in the myocardium in tuberculosis may be the result of a secondary nontuberculous infection. This seems the more logical because one occasionally finds myocarditis associated with other pulmonary lesions, not necessarily in bronchopneumonia alone but in bronchiectasis.[79] Whatever the explanation of such nonspecific myocarditis may be, it is important that the clinician be aware of the existence of the condition and try to recognize and evaluate it. In the light of our present knowledge, whether such myocarditis in children with tuberculosis is specific (tuberculous) or not seems unimportant from the clinical point of view.

An instance of an unusual form of myocardial involvement was described by Jones and Tilden.[80] An 11 year old girl entered the hospital because of tuberculous cervical adenitis. The pulse rate was 90 to 110 beats per minute, and the temperature varied from 98 to 99.8 F. The patient died suddenly, while drinking milk. The autopsy disclosed conglomerate tuberculosis of the myocardium, which had caused a tuberculous (mycotic) aneurysm at the base of the left ventricle. The sudden death resulted from rupture of the aneurysm and consequent hemopericardium.

Miliary Gummas and Gummatous Myocarditis.—Miliary gummas of the myocardium and myocarditis with miliary gummas apparently are extremely rare. It is interesting that the older literature contains a few more examples of syphilitic involvement of the myocardium in infants, obviously the result of congenital syphilis, than have been reported more recently. However, perhaps because of more adequate prenatal care and because of the relative ease with which the diagnosis of syphilis can be made in mothers and antisyphilitic treatment instituted, congenital syphilis is much less frequently encountered today than it was several decades ago. In regard to gummas we may quote Williams,[81] who studied a full term Negro girl who died three hours after birth. The Wassermann reaction of the mother was strongly positive. A number of oval, grayish white nodules were encountered in the myocardium. Countless spirochetes were found in sections stained by Levaditi's method. Though the diagnosis "gumma" was made grossly, microscopically the lesion was characterized by destruction of muscle and infiltration with lymphocytes, polymorphonuclear leukocytes, monocytes and plasma cells. Williams stressed the rarity of

77. Masugi, M.; Murasawa, S., and Yä-Shu: Ueber das Vorkommen von Aschoffschen Knötchen in Phthisikerherzen: Pathologisch-anatomische Beiträge zur Frage des Zusammenhangs zwischen Tuberkulose und Rheumatismus, Virchows Arch. f. path. Anat. **299**:426, 1937.

78. Auersbach, K.; Löwenstein, A., and Löwenstein, E.: Ueber symptomloses Vorkommen von Tuberkelbazillen im Tonsillengewebe bei rezidivierendem Gelenkrheumatismus und bei Neuritis retro-bulbaris, München. med. Wchnschr. **78**:1078, 1931.

79. Saphir, O.: Myocarditis in Bronchiectasis, Arch. Int. Med. **72**:775 (Dec.) 1943.

80. Jones, K. P., and Tilden, I. L.: Tuberculous Myocardial Aneurysm with Rupture and Sudden Death from Tamponade, Hawaii M. J. **1**:295, 1942.

81. Williams, J. W.: Multiple Gummas of the Heart in the Newborn, Am. J. Path. **6**:573, 1930.

gummas in the hearts of newborn infants. It is clear that, just as in adults, in instances of questionable syphilis the diagnosis of syphilitic myocarditis can be made only by finding the specific granuloma (gumma) or demonstrating the presence of Treponema pallidum. In general, it is believed that gummas, if present, may be found in either the auricular or the ventricular septum and may produce changes in the conducting system (Jagic [82]). Whether myocardial scars in a newborn infant in the absence of gummas and spirochetes can be regarded as syphilitic merely because the Wassermann reaction of the mother is positive and because there seems to be no other explanation for the scars is questionable.

Diffuse gummatous myocarditis is also extremely rare. Sohval,[83] in 1935, stated that only 7 instances could be found in the literature. Since that time a few other instances have been reported (Pratt-Thomas [84]). Recently Pratt-Thomas reported the case of a 2½ month old Negro girl, born of a syphilitic mother, who was first seen because of a cough and mild fever. Ten days later she was admitted to a hospital with the clinical diagnosis of pneumonia. The temperature was 103.2 F., and the pulse rate was 102. The Wassermann and Kline reactions were positive. At autopsy, in addition to pneumonia, diffuse gummatous myocarditis was found. No evidence of syphilis was found in any organ except the heart.

In the 97 cases of myocarditis which form the basis of this study, there was not a single instance in which the myocardial changes could be attributed to syphilis.

MYOCARDITIS IN MISCELLANEOUS DISEASES

There were 3 children in this series who, as shown at autopsy, had acute nephritis and also myocarditis. One of these children, a girl 12 years old, had bilateral hydronephrosis which became secondarily infected. The myocarditis obviously was the result of the secondary infection. In this instance a clinical diagnosis of myocarditis was made. The pulse rate was 120 and the temperature 98 F. Pyelonephritis was also encountered in the second patient, an 11 month old boy. The pulse was extremely rapid, and the temperature was 103 F. The third child, a boy 7 years old, had acute glomerulonephritis and died with uremia. He was sick only eight days. Microscopically, the myocarditis in the first and third patients was predominantly interstitial and diffuse. In the second patient, however, the inflammation was focal in type, with evidence of necrosis involving some of the muscle fibers. The culture of blood in this instance disclosed pneumococci type III.

The belief is occasionally expressed among clinicians that myocarditis occurs in patients with acute nephritis or with uremia. A survey of the more recent literature disclosed that myocardial inflammatory changes in uremia are rare and may be explained as an extension of uremic pericarditis into the adjacent portion of the myocardium. Such a condition, however, is not uremic myocarditis in the strict sense of the term. As for myocarditis in acute nephritis, it must be realized that, as in the instance just mentioned, it might well be caused by whatever caused the acute nephritis. Richter and O'Hare [85] emphasized that when fibrinous pericarditis is present the myocardium may present slight degeneration and mononuclear infiltration. Guthrie,[86] who studied nephritis in infants and children, stated that no pathologic changes were noted in the heart. Aldrich [87] reported 6 autopsies on children who died from acute postinfectious hemorrhagic nephritis. Myocarditis did not appear prominently among the lesions in these patients. In reporting 12 autopsies on children with chronic nonspecific nephritis in whom cardiac changes had been noted clinically, no reference was made to any myocardial lesions. Fishberg [88] stated that in a febrile patient with acute glomerulonephritis the myocardium may be injured by toxemia, although microscopic examination rarely reveals much change. From our experience, particularly that gained from the examination of the myocardium in adults with nephritis, we arrived at a similar conclusion.

There are several instances on record of myocarditis in virus and rickettsial diseases, blastomycosis and related diseases and helminthic diseases. However, to judge from the pertinent literature, such instances are extremely rare. (Myocarditis in poliomyelitis has been discussed in the section on infectious diseases.) There are a few instances on record of myocardial

82. Jagic, N.: Ein Beitrag zur Kasuistik des Adams-Stokesschen Symptomenkomplexes, Ztschr. f. klin. Med. **66**:183, 1908.

83. Sohval, A. R.: Gumma of the Heart, Arch. Path. **20**:429 (Sept.) 1935.

84. Pratt-Thomas, H. R.: Diffuse Gummatous Myocarditis, Arch. Path. **36**:80 (July) 1943.

85. Richter, A. B., and O'Hare, J. P.: The Heart in Chronic Glomerular Nephritis, New England J. Med. **214**:824, 1936.

86. Guthrie, K. J.: A Study of the Pathology of Nephritis in Infancy and Childhood, J. Path. & Bact. **42**:565, 1936.

87. Aldrich, C. A.: Nephritis, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1937, vol. 3.

88. Fishberg, A. M.: Hypertension and Nephritis, ed. 4, Philadelphia, Lea & Febiger, 1939.

changes in toxoplasma infection in children (Pinkerton and Weinman [89]). Though not particularly in children, myocarditis has been reported in typhus and in Rocky Mountain spotted fever. Hertig [90] reported a 10 day old white girl whose myocardium contained sarcosporidia. Blastomycosis involving the myocardium is recorded by Baker and Brian,[91] who reviewed the literature. Actinomycosis should also be mentioned; Harbitz and Gröndahl [92] found such an infection in a 14 year old boy who died suddenly after an illness of nine months. Edwards,[93] who discussed actinomycosis in children, mentioned a 10 year old boy for whom a clinical diagnosis was made of sarcoma of the liver with metastases to the lungs. Before death, signs of cardiac failure developed. Autopsy disclosed actinomycosis of the upper and anterior mediastinum, which was fused with the pericardium, lung and sternum. There was an extension of the characteristic granulation tissue through the myocardium into the ventricular cavity, and there were numerous minute ulcers in the myocardium.

Gordon, Cares and Kaufman [94] reported an instance of myocarditis associated with trichinosis in a 14 year old girl. There was a rough systolic murmur, localized at the apex. The myocardial sounds were of fair muscular quality and regular in rhythm. There were also signs and symptoms of encephalitis, the disease from which the patient seemingly died. The autopsy disclosed myocarditis in addition to encephalitis. Though no larvae were found in the myocardium, they were present in the diaphragm and in the psoas and rectus abdominis muscles. From the literature it is evident that myocarditis in infections with Trichinella spiralis is occasionally encountered. The myocarditis usually occurs between the fourth and the sixth week after the infection, or, at least, death occurs at that time. From experimental studies it appears probable that the larvae are present in the myocardium about a week after the infection occurs and then disappear from the myocardium, though there are a few instances on record in which the larvae were found in the myocardium as late as the twenty-ninth day. With the knowledge that myocarditis may occur in trichinosis it becomes imperative to examine the diaphragm and the skeletal muscles in every instance of myocarditis in which the cause is not apparent.

Myocardial inflammatory changes in hyperthyroidism and in hypothyroidism are also reported in the literature. However, myocardial changes in these diseases are principally degenerative. True myocarditis is rarely encountered. The same may be said of the myocardial changes found in vitamin deficiency diseases and in hypervitaminosis. Serous myocarditis as sometimes found in beriberi was discussed previously.

From our study it is evident that myocarditis in children may and does occur as the result of various acute infectious processes. In our series it was noted in 97 of 1,420 autopsies, an incidence of 6.83 per cent.

Of the 60 patients whose clinical records were available, a clinical diagnosis of myocarditis was made for only 10, 7 of whom were children who presented the clinical picture of rheumatic heart disease. At autopsy, 4 of these 7 showed typical rheumatic myocarditis, and 3 showed what was termed a "rheumatic type of myocarditis." In 1 instance a diagnosis of myocarditis was made for a patient with poliomyelitis. We feel it is interesting that this diagnosis was made after the attending pediatrician had become familiar with some recent work on myocarditis in poliomyelitis. The remaining 2 patients for whom the clinical diagnosis of myocarditis was made had infected hydronephrosis and pyemia, respectively, with multiple abscesses in the myocardium.

From a review of our clinical records it is clear that no definite criteria can be laid down for the clinical diagnosis of acute myocarditis, since it often runs its course without producing any symptoms which may make diagnosis possible.

Although there are no characteristic symptoms, a study of the clinical courses of our patients leads us to make the following observations. Myocarditis may be suspected if a patient with an infectious disease suddenly becomes worse and begins to fail without apparent reason. Tachycardia out of proportion to the temperature is the most significant single symptom. This was present in 30 of the 60 patients for whom we had complete records. Occasionally, however, the pulse rate was much slower than normal. The pulse may be feeble and is often irregular. Cardiac enlargement is frequently present. It was noted clinically in 35 of

89. Pinkerton, H., and Weinman, D.: Toxoplasma Infection in Man, Arch. Path. **30**:374 (July) 1940.

90. Hertig, A. T.: Sarcosporidia in Myocardium of Premature Infant: Report of Case, Am. J. Path. **10**: 413, 1934.

91. Baker, R. D., and Brian, E. W.: Blastomycosis of the Heart, Am. J. Path. **13**:139, 1937.

92. Harbitz, F., and Gröndahl, N. B.: Die Strahlenpilzkrankheit (aktinomykose) in Norwegen: Studien über ihr Vorkommen; ihre Lokalisation und Bakteriologie, Beitr. z. path. Anat. u. z. allg. Path. **50**:193, 1911.

93. Edwards, A. C.: Actinomycosis in Children, Am. J. Dis. Child. **41**:1419 (June) 1931.

94. Gordon, M. B.; Cares, R., and Kaufman, B.: Encephalitis and Myocarditis in a Fatal Case of Trichinosis, J. Pediat. **6**:667, 1935.

our cases. In 29 of these the condition was diagnosed as rheumatic heart disease and bacterial endocarditis. In the instances in which it was recorded, the arterial blood pressure was usually low. The action of the heart may be disturbed, and an electrocardiogram will often reveal significant changes. Electrocardiograms were taken for 22 of our patients, 19 of whom showed definite evidence of myocardial involvement. Cyanosis, particularly if associated with tachycardia, is significant. It was present 11 times in our series.

Sudden death is not unusual in myocarditis. Of our 60 patients, 9 died suddenly.

Clinically, evidence of heart failure was noted in 32 cases. In the vast majority of the 32 cases the condition was diagnosed as rheumatic heart disease. Autopsy disclosed that 15 of the 32 patients had rheumatic myocarditis and that 8 had a "rheumatic type" of myocarditis. Three other children had subacute bacterial endocarditis and 3 had uncomplicated bronchopneumonia. The remaining 3 children had postdiphtheritic myocardial involvement (reparative myocarditis), bacterial endocarditis with myocarditis and isolated myocarditis, respectively.

SUMMARY

In 1,420 autopsies on children between the ages of 8 days and 16 years 97 instances of myocarditis were observed, an incidence of 6.83 per cent. This disease was encountered 150 times in 3,712 autopsies performed on adults during the same period, an incidence of 4.05 per cent. These figures represent myocarditis seen in a general pediatric hospital. Types of myocarditis occurring during the course of contagious diseases are not included; references to these, however, are made in the discussion.

Among the 97 cases of myocarditis, there was 1 in which the condition was diagnosed as postdiphtheritic inflammation of the myocardium. Myocarditis was associated with meningitis in 4 cases, with poliomyelitis in 7, with bronchopneumonia in 12, with lobar pneumonia in 3 and with nephritis in 3. Abscesses in the myocardium, associated with various infectious diseases and various portals of entry, were present in 16 instances. Myocarditis associated with bacterial endocarditis was present 5 times; myocarditis associated with subacute bacterial endocarditis, 7 times. There were 13 instances of a "rheumatic type" of myocarditis. Rheumatic myocarditis was present 19 times, isolated myocarditis 3 times and myocarditis in tuberculosis 4 times.

Fetal myocarditis, with the exception of myocarditis in congenital syphilis, if it occurs at all is extremely rare. The essential myocardial lesion in diphtheria is parenchymatous hyaline degeneration or necrosis. Later there occurs a reparative inflammatory process. It is questionable whether the latter should be considered true myocarditis. Myocarditis in measles is rarely encountered; nor does myocarditis occur frequently in mumps, whooping cough, smallpox or varicella. It seems that inflammatory myocardial damage occurs much more often in scarlet fever than has been heretofore believed. Perhaps a parallel statement would be true for a number of other contagious diseases if further studies were made of the myocardium in such conditions. Myocarditis is also observed in epidemic meningitis and poliomyelitis. In the latter disease it seems to occur more frequently than is generally accepted. In bronchopneumonia and lobar pneumonia it is occasionally encountered. In pyemia, abscesses of the myocardium occur relatively frequently; however, a cursory examination of the myocardium often fails to disclose small abscesses.

Isolated myocarditis occasionally occurs in children who have no other disease that may be considered as the source of the myocarditis. Occasionally this form of myocarditis has been found associated with exanthematous diseases. It may cause sudden death in children who had been apparently healthy and in whom progressive myocardial weakness developed, more or less quickly. Anatomically it does not vary in histologic details from myocarditis in acute infectious diseases.

Myocarditis in bacterial and subacute bacterial endocarditis is often encountered and rarely diagnosed clinically. In rheumatic endocarditis and the "rheumatic type" of endocarditis myocarditis occurs frequently. This is the only type of myocarditis recognized and diagnosed clinically with any degree of frequency.

Miliary tubercles are found only occasionally in cardiac muscle. There is a type of myocarditis which occurs in tuberculosis without the formation of the typical granulation tissue. It is evident that this nonspecific myocarditis cannot be called tuberculous. In the older literature miliary gummas and gummatous myocarditis are reported to occur in infants with congenital syphilis. At present they seem to be encountered rarely.

Myocardial damage in uremia is rare and may be explained by an extension of uremic pericarditis into the adjacent myocardium. Whatever may have caused the nephritis may cause the myocarditis. Myocarditis in trichinosis, blastomycosis and virus, rickettsial and various other diseases is also mentioned.

Clinically, myocarditis may be suspected if during the course of an infectious disease a child suddenly becomes worse and begins to fail without apparent cause. Tachycardia out of proportion to the temperature, particularly if accompanied by cyanosis, is an early sign that may direct attention to the myocardium. Cardiac enlargement is frequently present, and the blood pressure is usually low. The electrocardiogram sometimes reveals significant changes.

In 97 instances of myocarditis evidence of heart failure was noted 32 times. In the vast majority of these cases a diagnosis of rheumatic heart disease was made. Sudden death of patients with myocarditis was not unusual; 9 out of 60 children died suddenly.

From our study it is evident that myocardial damage in children may and does occur in diseases other than rheumatic fever and diphtheria. The incidence of myocarditis in our series (6.83 per cent) indicates clearly that the possible occurrence of myocarditis during the course of an infectious disease must be borne in mind. The possibility of myocarditis having once been considered, further investigation may reveal additional confirmatory evidence. Perhaps the relatively high incidence of the clinical diagnosis of myocarditis for patients with rheumatic heart disease can be explained by the fact that it is generally accepted that myocarditis often occurs in patients with rheumatic heart disease.

The incidence of myocarditis as determined by routine examination of the heart is seemingly low. However, we suspect, especially from our experience with myocarditis in poliomyelitis, that myocarditis in general would be found frequently and would no longer be regarded as a rare condition if the myocardium were carefully examined histologically for the purpose of ruling out or substantiating the presence of inflammatory disease.

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Abstracts from Current Literature

Biochemistry; Bacteriology, and Pathology

BIOCHEMICAL AND ANTIGENIC RELATIONSHIPS OF THE PARACOLON BACTERIA. C. A. STUART, K. M. WHEELER, ROBERT RUSTIGIAN and ALICE ZIMMERMAN, J. Bact. **45**:101 (Feb.) 1943.

The authors studied the biochemical and serologic relationships of the paracolon organisms among themselves, to normal coliform bacilli and to Salmonella. An extensive investigation was made, and the results may be of some value to the practical bacteriologist. The paracolon organisms were defined as a group of aberrant coliform organisms isolated from man and comprising a distinct biologic group of bacteria. There was some evidence of geographic segregation in the paracolon group, since with few exceptions strains from one locality were frequently identical with other cultures from the same locality but seldom with strains from a different one. The pathogenicity of the paracolon bacteria was not proved, but the authors found them often associated with mild or acute gastroenteritis of short duration. For further details reference to the original article is recommended.

STOESSER, Minneapolis.

THE EFFECT OF PLEURAL EFFUSIONS ON THE GROWTH OF STAPHYLOCOCCUS AUREUS IN VITRO. ALICE B. TOMLER and MAX PINNER, J. Bact. **45**:341 (April) 1943.

It may be of interest to know that suppurative lesions due to Staphylococcus aureus do not occur in the presence of tuberculous effusions. The subject has been studied by the authors, and their experiments appear to indicate that the inhibition of growth of this organism in the presence of tuberculous pleural effusion is apparently due to an actively inhibitory factor and not to deficiency in nutritive qualities. They draw this conclusion from the following observations: When a small percentage of nutrient broth is added to effusions, the growth is poorer than in the same percentage of nutrient broth in a solution of sodium chloride; such a dilution of effusions by saline solution tends to decrease their inhibitory action; inhibition is diminished by shaking the effusions during the period of growth, and inactivated effusions inhibit less.

STOESSER, Minneapolis.

SYLVATIC PLAGUE STUDIES: II. THE FATE OF PASTEURELLA PESTIS IN THE FLEA. J. R. DOUGLAS and C. M. WHEELER, J. Infect. Dis. **72**:18 (Jan.-Feb.) 1943.

White mice when inoculated intraperitoneally with a relatively small number (20,000) of organisms of Pasteurella pestis, as a rule, have a maximal bacteremia of 10,000,000 organisms per cubic millimeter of blood about forty-eight hours after infection.

Approximately 60 per cent of infected Diamanus montanus and 2 per cent of Xenopsylla cheopis apparently are able to free their alimentary canals of Pasteurella pestis after single meals of infectious blood. In Diamanus montanus this may occur within twenty-four hours after infection. In Xenopsylla cheopis the process requires more than forty-eight hours.

P. pestis may multiply in the esophagus, proventriculus and stomach of both species of fleas. The esophagus of Diamanus montanus is invaded twice as frequently as that of Xenopsylla cheopis. Occlusion of the lumen of the alimentary tract by P. pestis requires an average of ten days in the first-named species and sixteen days in the second.

The excretion of viable P. pestis in the feces of infected Diamanus montanus and Xenopsylla cheopis is extremely irregular. Fifty-six per cent of the daily fecal samples of infected Diamanus montanus and 25 per cent of samples from Xenopsylla cheopis yield viable organisms. P. pestis is present in very small numbers of viable organisms in infected feces, averaging 200, with a maximum of 400 and a minimum of less than 10, for a twenty-four hour period.

TOOMEY, Cleveland.

ISOLATION AND PROPERTIES OF THE EQUINE ENCEPHALOMYELITIS VIRUS (EASTERN STRAIN). A. R. TAYLOR, G. D. SHARP, DOROTHY BEARD and J. W. BEARD, J. Infect. Dis. **72**:31 (Jan.-Feb.) 1943.

A liponucleoprotein complex has been isolated by ultracentrifugal procedures from extracts of chick embryos diseased with the virus of equine encephalomyelitis (Eastern strain). The purified material behaves as the virus in the induction of the characteristic disease in animals. The quantity of material isolated represented 0.5 of 1 per cent of the total protein of the chick embryo extracts. The degree of concentration with respect to protein was about one hundred times, and with respect to the weight of embryo tissue extracted, about two thousand times. The infectivity of the purified preparations parallels that of the crude extracts from which they were derived.

TOOMEY, Cleveland.

STUDIES ON THE ACTIVITY OF SODIUM SULFADIAZINE AGAINST BACTERIUM TULARENSE: I. TREATMENT OF EXPERIMENTAL TULAREMIC INFECTION IN THE CHICK EMBRYO. JOHN CHRISTIAN RANSMEIER, J. Infect. Dis. **72**:77 (Jan.-Feb.) 1943.

Sodium sulfadiazine administered intra-amniotically or by way of the chorioallantoic membrane in doses of 10 mg. appeared to exert little, if any, effect on the course of the infection produced in the developing chick embryo by subsequent chorioallantoic inoculation with Bacterium tularense.

FROM THE AUTHOR'S SUMMARY.

STUDIES ON THE ACTIVITY OF SODIUM SULFADIAZINE AGAINST BACTERIUM TULARENSE: II. EFFECT ON GROWTH IN VITRO. JOHN CHRISTIAN RANSMEIER, J. Infect. Dis. **72**:83 (Jan.-Feb.) 1943.

Sodium sulfadiazine added to slants of blood-dextrose-cystine agar in concentrations of 50, 100 and 200 mg. per hundred cubic centimeters exerted a definite and increasingly pronounced inhibitory effect on the growth of Bacterium tularense. No inhibition was observed in the presence of 10 or 20 mg. of the drug per hundred cubic centimeters.

The amount of hydrogen sulfide produced from such slants was proportional to the degree of growth. Sodium sulfadiazine appeared to exercise no specific action on this process. TOOMEY, Cleveland.

THE REACTION OF THE CHICK EMBRYO TO VIRULENT AND NONVIRULENT STRAINS OF BACTERIUM TULARENSE. JOHN CHRISTIAN RANSMEIER, J. Infect. Dis. **72**:86 (Jan.-Feb.) 1943.

A rather constant reaction can be produced in fourteen day incubated chick embryos with virulent strains of Bacterium tularense, resulting in death within seventy-two to one hundred and twenty hours after inoculation.

Chick embryos of fourteen days' incubation appear suitable for studies of virulence and of therapeutic agents with B. tularense. The variable accidental mortality makes the use of adequate numbers of controls essential. TOOMEY, Cleveland.

Metabolism; Infant Feeding; Milk and Other Foods

AN OUTBREAK OF ACUTE FLUORIDE POISONING. H. S. INGRAHAM and A. J. FLOOD, New York State J. Med. **43**:41 (Jan. 1) 1943.

Seventy-one inmates in a state reform school were poisoned by sodium fluoride in chocolate pudding. The usual severe gastrointestinal symptoms developed, but there were no deaths. An inmate who acted as a cook later admitted that "he had scooped up as much roach powder as he could hold in one hand and cast it into the pudding to get even with another inmate." AIKMAN, Rochester, N. Y.

NITROGEN BALANCE IN EXPERIMENTAL HUMAN DEFICIENCIES OF METHIONINE AND CYSTINE. ANTHONY A. ALBANESE, L. EMMETT HOLT JR., JOSEPH BRUMBACK JR., CHARLOTTE N. KAJDI, JANE E. FRANKSTON and DOROTHY M. WANGERIN, Proc. Soc. Exper. Biol. & Med. **52**:18 (Jan.) 1943.

Three human adult subjects (two men and a woman) were maintained first on a diet deficient in the amino acid methionine and later on a diet poor in cystine. There were a decrease in weight and a negative nitrogen balance in each subject when maintained on the diet low in methionine, but none of the 3 exhibited any signs or symptoms of disease during the twenty-four day period. When the diet was low in cystine both the men lost weight and 1 had a negative nitrogen balance, whereas the woman maintained her weight and remained in nitrogen equilibrum. From these data the authors feel that methionine may be regarded as a human dietary essential whereas cystine may not be regarded as such. HANSEN, Minneapolis.

DERMATITIS ON A SYNTHETIC RATION ADEQUATE FOR GROWTH AND REPRODUCTION IN THE RAT. BENJAMIN H. ERSHOFF, Proc. Soc. Exper. Biol. & Med. **52**:41 (Jan.) 1943.

Rats reared on a diet of sucrose, vitamin test casein (S.M.A.), cystine and salt to which were added thiamine, pyridoxine, riboflavin, nicotinic acid, calcium pantothenate, paraaminobenzoic acid, inositol, choline, corn oil, alpha tocopherol and vitamins A and D concentrates acquired a specific dermatitis of the tail. It is suggested that some dietary factor independent of pantothenic acid, pyridoxine or essential fatty acid is necessary for the maintenance of normal epithelium of the tail. HANSEN, Minneapolis.

STUDIES WITH DOGS MAINTAINED ON DIETS LOW IN FAT. ARILD E. HANSEN and HILDA F. WIESE, Proc. Soc. Exper. Biol. & Med. **52**:205 (March) 1943.

At weaning, 8 litter mate puppies were given a diet low in fat (0.13 per cent) composed of skim milk, cottage cheese, polished rice and sucrose supplemented with vitamins, bone ash and salt mixtures. Four of the puppies served as control animals and received lard substituted for sucrose to the extent of 28 per cent of the total calories. When the puppies were about 3 months of age, the skin of the animals on the low fat diet showed large scales and flaky desquamation and the hair was dry and coarse. The skin and hair of the control animals remained clear and soft. At the same time the iodine number of the serum fatty acids of the animals on the low fat diet was definitely lower than that of the serum fatty acids of the control dogs. This was true for the fatty acids in both the acetone-soluble and the acetone-insoluble fraction, but the greater difference appeared in the acetone-soluble fraction, the average iodine number being 83.9 for the dogs receiving practically no fat compared with 118.7 for the dogs receiving lard in the diet. Animals on the low fat diet synthesized sufficient fat to maintain a fat level in the serum equal to that of the animals receiving fat in the diet, but judging from the iodine number of the fatty acids the composition of the synthesized fatty acids was materially different from that of the acids in the fat appearing in the serum of the control animals. HANSEN, Minneapolis.

A BIOCHEMICAL LESION OF LYSINE DEFICIENCY IN MAN. ANTHONY A. ALBANESE, L. EMMETT HOLT JR., JANE E. FRANKSTON, CHARLOTTE N. KAJDI, JOSEPH E. BRUMBACK JR. and DOROTHY M. WANGERIN, Proc. Soc. Exper. Biol. & Med. **52**:209 (March) 1943.

Three adult human subjects were maintained on a diet deficient in lysine. After five days on this diet all 3 subjects complained of nausea, dizziness and hypersensitivity to metallic sounds. No objective signs were discovered by clinical examination. A definite negative nitrogen balance developed in all 3 patients, and the level of the urinary nonketonic organic acids rose sharply. When a pancreatic digest of casein fortified with 1 per cent l-cystine was given, within four days the subjective symptoms were relieved, nitrogen equilibrium was restored and the amount of organic acids excreted fell to normal. Essentially the same conditions resulted when these studies were repeated for 2 of the 3 original patients. The increase in the urinary excretion of nonketonic organic acids appears to be characteristic of lysine deficiency and is not due to a negative nitrogen equilibrium per se. The nature of the organic acid excreted in the urine is being studied. HANSEN, Minneapolis.

SECRETION OF RADIOACTIVE SODIUM IN HUMAN MILK. W. T. POMMERENKE and P. F. HAHN, Proc. Soc. Exper. Biol. & Med. **52**:223 (March) 1943.

Four normal women from 20 to 25 years of age in the early postpartum state were given 65 mg. of radio-

active sodium as the chloride in orange juice, and one breast was emptied with a pump at frequent intervals. The radioactive sodium was recovered in milk within twenty minutes after its ingestion. The peak concentration was reached in two hours, and gradual tapering off occurred in that some sodium could be recovered after ninety-six hours. HANSEN, Minneapolis.

FLUORINE DISTRIBUTION. C. N. BROMEHEAD, MARGARET M. MURRAY and DAGMAR C. WILSON, Lancet **1**:490 (April 17) 1943.

In view of the increasing evidence of the role of fluorine in the well-being of man and of animals, methods are suggested to assist the clinician in understanding the distribution of fluorine. Geologically, fluorine may be found in association with fluorspar, apatite and phosphate-bearing rocks and Jurassic clays. Mottled enamel as a sign of dental fluorosis can be used as an index of absorption of fluorine. These two indications of the likely intake of fluorine in any particular locality may be further substantiated by chemical determination of fluorine in the drinking water.

LANGMANN, New York. [AUTHORS' SUMMARY.]

DISCUSSION ON WATER METABOLISM IN SICK AND HEALTHY INFANTS. WINIFRED F. YOUNG and R. A. MCCANCE, Proc. Roy. Soc. Med. **36**:218 (March) 1943.

A full summary of the discussion by W. F. Young and R. A. McCance on metabolism of water in sick and in healthy infants is given in the report. Avery Jones and Richard Dobbs made a few comments at the close of the paper. WILLIAMSON, New Orleans.

Vitamins; Avitaminoses

THE EFFECT OF VARIOUS STAGES OF VITAMIN A DEFICIENCY IN THE WHITE RAT ON THE RESISTANCE TO NIPPOSTRONGYLUS MURIS. EDWIN G. RILEY, J. Infect. Dis. **72**:133 (March-April) 1943.

A decrease in resistance to infection with Nippostronglyus muris in A-avitaminotic white rats, found by Spindler, is confirmed. The decrease in resistance does not become evident until the rats have been on the deficient diet for four weeks. After two weeks of depletion of vitamin A there is actually an increase in resistance to infections. The latter decrease manifests itself by a more intense and prolonged infection.

Immune serum is relatively as effective in decreasing the peak of infection in both normal and deficient rats, although in the latter many of the worms may merely be slowed in their migration through the body of the host. TOOMEY, Cleveland.

THE VITAMIN B COMPLEX OF PEELED WHEAT BREAD. ROBERT R. SEALOCK and ARTHUR H. LIVERMORE, J. Nutrition **25**:265 (March) 1943.

Sealock and Livermore, by means of standard assay procedures, determined the content of various members of the vitamin B complex in bread made with flour from peeled wheat. Detailed results are presented in three tables. "The values obtained in micrograms per gram of fresh bread are thiamine 3.0, riboflavin 2.5, nicotinic acid 35, pantothenic acid 5.2, pyridoxine 3.1 and inositol 644." FREDEEN, Kansas City, Mo.

THE NICOTINIC ACID CONTENT OF COMMON FRUITS AND VEGETABLES AS PREPARED FOR HUMAN CONSUMPTION. WALTER C. RUSSELL, M. WRIGHT TAYLOR and JACK F. BEUK, J. Nutrition **25**:275 (March) 1943.

By means of the microbiologic method, the content of nicotinic acid was determined for several vegetables and fruits. The detailed results are presented in five tables. The content of nicotinic acid was highest in fresh peas, asparagus and avocadoes, and lowest in certain of the fruits and fruit juices.

FREDEEN, Kansas City, Mo.

ASCORBIC ACID AND COMPLEMENT—A STUDY OF THEIR RELATIONSHIP. JAMES DEENY, ERIC T. MURDOCK and JOHN J. ROGAN, Irish J. M. Sc., March 1943, p. 86.

There was no relationship between complement and ascorbic acid in different forms of acute infection. The level of ascorbic acid in the blood bore no relationship to the patient's recovery from acute infection or his resistance to disease. SNELLING, Toronto, Canada.

EFFECT OF BONE DYSPHASIA ON CRANIAL NERVES IN VITAMIN A-DEFICIENT ANIMALS. E. MELLANBY, J. Physiol. **101**:408 (March 25) 1943.

When young dogs are brought up on diets deficient in vitamin A and carotene, local overgrowth of certain bones of the skull causes compression, twisting and lengthening of most of the cranial nerves, some of which show extensive degenerative changes. The destructive changes are chiefly confined to the sensory nerves, the motor cranial nerves for the most part escaping. Motor nerves often suffer compression, lengthening and twisting as a result of overgrowth of bone, but show no degeneration.

In the experiments described, the nerves most affected were the cochlear and vestibular divisions of the eighth cranial nerve, especially the former, the first and second branches of the fifth cranial nerve and the second and first cranial nerves. Apparently, the reason for the greater susceptibility of the sensory nerves lies in the compression not only of the nerve fibers but of the ganglions.

Degeneration in the optic nerve may be produced in vitamin A deficient animals not only by direct pressure of overgrown bone and by increased intracranial pressure but by a primary degenerative change, beginning in the retina itself. The early atrophy of the optic nerve associated with bleaching of the tapetum is probably a direct effect of the vitamin A deficiency on retinal cells.

In experiments in which the calcium intake was high the increased growth of certain bones appeared to be due to formation of an excess of cancellous tissue.

THOMAS, Philadelphia. [ARCH. NEUROL. & PSYCHIAT.]

Hygiene; Growth and Nutrition; Public Health

THE EFFECT OF THE WAR ON THE MATERNAL WELFARE PROGRAM IN ILLINOIS. FREDERICK H. FALLS, Illinois M. J. **83**:259 (April) 1943.

The outlook in the immediate future is anything but rosy for further progress in the work of the Maternal Welfare Committee, or even for holding the gains that have been made.

The care of the wife and the baby of the man who has left for service with the armed forces is an especially important obligation of the state. Nothing that could be done for such a man would do more to bolster his morale and increase his efficiency than to know that the best medical service possible under the circumstances will be available to his family, as a result of intelligent planning by the people whose life and liberty he is called on to defend. Such a man should not have to worry about anything except his job as a soldier. It is a small return for his sacrifices for the community in which he lives to insure adequate care and protection for his wife and babies, even at considerable personal sacrifice.

BARBOUR, Peoria, Ill.

THE QUESTION OF MORTALITY IN INFANTS AND CHILDREN IN INDIA, LAYING SPECIAL EMPHASIS ON MEASURES TO CONTROL IT. B. M. DUBASH, J. Indian M. A. **12**:175 (April); 201 (May) 1943.

The author presents an excellent exposition of the factors responsible for, and of the methods of reduction of, infant and child mortality.

GONCE, Madison, Wis.

HEIGHT AND WEIGHT MEASUREMENTS OF SCHOOL CHILDREN. Z. BENJAMIN, J. Hyg. **43**:55 (Jan.) 1943.

Benjamin reports the results of a study of 4,000 London elementary school children during the period 1935 to 1938. This study confirms previous work indicating that the maximum increase in height is reached in the latter part of spring and that of weight in the latter part of autumn, with its minimum in the spring.

JANNEY, Wauwatosa, Wis.

INFANT MORTALITY IN RIO DE JANEIRO, BRAZIL. NOTE, Arch. de pediat. **14**:521 (Sept.) 1942.

This note reports that in the last thirty-five years the infant mortality in Rio de Janeiro has been around 180 per thousand. Detailed figures are given for the years 1903 to 1938.

LOZOYA S., Mexico, Mexico.

PROTECTION OF CHILDREN IN DANGER ZONES AND PLANNING FOR CARE OF CHILDREN AFTER EVACUATION ARISING FROM MILITARY NECESSITY. MARTHA M. ELIOT, Bol. Inst. internac. am. de protec. a la infancia **16**:324 (Jan.) 1943.

The protection of children in danger zones and their removal to areas of safety if necessary are the responsibility of government. Experience of countries which have undergone bombing is of great value to those faced with such a possibility, though each country will need to adjust plans to its own peculiar circumstances. The maintenance of essential services—health, welfare and education—is fundamental to civilian protection. The success of any plan for evacuation depends on adequate preliminary planning and preparation, especially for reception care. The most difficult aspect of evacuation is the process of placement and continuing care. To accomplish this satisfactorily it is necessary to make a preliminary review of facilities in an area to be used for reception and provision for supplementing them when necessary with personnel and services in the fields of health, welfare, education and recreation.

[EDITOR'S SUMMARY.]

PROGRESS IN THE DEVELOPMENT OF SERVICES FOR EDUCATION AND RECREATION. HAROLD BENJAMIN, Bol. Inst. internac. am. de protec. a la infancia **16**:345 (Jan.) 1943.

This address, presented before the eighth Pan-American Child Congress, is a general discussion of the development of educational facilities and requirements from 1935 to 1942 in the pan-American countries.

There seems to be a definite tendency in all of the countries to emphasize training for citizenship. Better facilities are being offered for children with special disabilities, although these facilities are still inadequate. Recreational programs, health measures and school feeding projects have had widespread development. Occupational education has also increased. In conclusion, Dean Benjamin looks forward to still greater improvement in the next seven years, with emphasis on a better selection of teachers, which must be helped by a better appreciation in the community of the profession of teaching.

LESLIE, Evanston, Ill.

THE ACTIVITY SCHOOL AND RURAL CULTURE. RAMÓN I. CARDOZO, Bol. Inst. internac. am. de protec. a la infancia **16**:357 (Jan.) 1943.

At first the author emphasizes the meaning of culture in its integral sense, embracing the whole of man's life; he afterward refers to the executive plan of the activity school, to methods that should be employed in rural education and to standards and policies related to intellectual development.

With regard to Paraguay, he specially points out the social environment which leads people to engage in different handiworks, so that the introduction of manual labor in the curriculum implies the fitness of the school to the environment. Moreover he thinks the collaboration of the community should be sought, so that if the school receives contributions from the neighborhood it may by reflective action report benefits to youth and adults.

He ends by establishing that the activity school with all its resources may supply culture to the rural population and improve its spiritual life, acting directly through children or indirectly through the family.

[EDITOR'S SUMMARY.]

PURPURA OF SCHOENLEIN-HENOCH. JUAN FLOR JORGANES, Medica, Mantazas **2**:34 (Jan.-Feb.) 1943.

The author presents the case of a 5 year old child with nonthrombopenic purpura of unknown cause (Schoenlein-Henoch purpura). The history, physical signs and laboratory analysis are reported. Progress notes reveal an illness lasting twelve days, with spontaneous recovery. The author concludes, from a consideration of the purpuric cutaneous lesions, acute edema, painful motion of joints, lack of alteration in the blood and positive Rumpel-Leede sign, that this is a case of nonthrombopenic purpura of unknown cause.

ZETTELMAN, Evanston, Ill.

PREVENTIVE ACTIVITIES OF MEDICAL INSPECTION IN SCHOOLS FOR COMBATING THE PROBLEMS OF SEPTIC FOCI IN SCHOOL CHILDREN. RAMON LORENZO, Rev. de hig. y med. esc. **2**:59, 1943.

The function of medical inspection of schools is primarily prophylactic and preventive and secondarily curative.

The author stresses the necessity of awakening parents to the seriousness of dental and tonsillar septic foci and of the conditions which may develop if they are disregarded.

Physician, radiologist and dentist must collaborate closely in the identification of dental septic foci. Of 1,027 school children attending the first grade, 904 (89 per cent) were found to have dental decay. It is presumed that these children must have a deficiency of vitamins C and D.

Another source of oral sepsis is hypertrophic septic tonsils. The author discusses the pathologic conditions which may arise from this focal infection and presents statistics to show the frequency of tonsillar sepsis among school children. Of 896 children, 123 (13.7 per cent) had hypertrophic and septic tonsils.

[From the Author's Summary.]

Prematurity and Congenital Deformities

Care of the Premature Infant. Harry S. Snyderman, M. Rec. **156**:151 (March) 1943.

Separate rooms, properly heated and humidified, good nursing care, gentle handling, careful choice and administration of foods with preference for breast milk and biolac and avoidance of infection by strict isolation technic are stressed in the care of the premature infant.

In the treatment of cyanosis in the premature infant, from whatever cause, administration of oxygen at a rate of 3 liters per minute is by far the most effective therapy. Fluctuations in temperature may occur from infections, intracranial hemorrhage and other causes. Gentleness, warmth, rest, administration of oxygen, blood and vitamin K and good nursing are suggested for handling these variations.

Gastrointestinal upsets are most commonly the result of overfeeding, rough or too frequent handling, improper formulas or improper methods of feeding and infections of the upper respiratory tract. Vomiting and diarrhea with abdominal distention, fever or sometimes subnormal temperature and prostration are best treated by a period of starvation. During the starvation period 5 per cent dextrose solution should be given by clysis, along with blood transfusions and then the infant should gradually be given breast milk or a proper formula.

Ferdinand, Peoria, Ill.

Newborn

Erythroblastosis Fetalis and the Blood Factor Rh. Donald H. Kariher and Howard A. Spindler, Am. J. M. Sc. **205**:369 (March) 1943.

Six cases of erythroblastosis fetalis are presented in which the mothers were immunized by Rh agglutinogen from the fetus.

In 1 of these cases, by means of Rh studies on the mother ante partum the subsequent delivery of an erythroblastotic infant was anticipated, and the infant was given numerous transfusions of Rh-negative, anti-Rh-negative blood. This line of therapy is recommended in all cases of erythroblastosis.

A case of "habitual abortion" is described in which the absence of the Rh factor in the mother seemed to be the cause.

It is suggested that the term "erythroblastosis" be dropped and that the conditions known as icterus gravis, fetal hydrops and hemolytic anemia be included under the term "hemolytic disease of the newborn."

Henske, Omaha.

Disorders of the Newborn. Samuel E. Kohn, Wisconsin M. J. **42**:404 (April) 1943.

This is a review of the causes, symptoms and treatment of the more common difficulties of the newborn. Prompt and thorough care along generally accepted lines is urged. Ten to 15 per cent of deaths in the first few days of life are due to pneumonia. Early surgical and supportive measures are advised in cases of pyloric stenosis to avoid the serious effects of dehydration and intoxication. Janney, Wauwatosa, Wis.

Treatment of Asphyxia of the Newborn by Administration of Carbon Dioxide to the Mother. R. Schwarcz, F. Nessi and R. Pinto, Rev. Asoc. méd. argent. **57**:166 (April 15-30) 1943.

The authors state that neonatal asphyxia can largely be obviated and can be treated by the administration of carbon dioxide to the mother. They briefly review the mechanism of the establishment of respiration after birth and suggest that the physiologic apnea may easily become a dangerous anoxia with damage to tissue. They further suggest that a fetus impregnated by an anesthetic, depressed by a hypnotic and with a sectioned umbilical cord may have trouble in establishing repiration. They therefore advise inhalations of carbon dioxide for the mother, before sectioning of the umbilical cord, to increase the amplitude of respirations and eliminate the anesthetic. This sequence of events is transmitted to the infant and results in rapid initiation of respiration.

Thirty-six clinical obstetric cases are presented, with good results in all but 3.

The authors warn that before carbon dioxide inhalation can result beneficially the following conditions must be present: (1) integrity of the fetal-maternal circulation, (2) noninjured fetal respiratory center, (3) clear fetal air passages and (4) distensible fetal lungs.

Zettelman, Evanston, Ill.

Acute Contagious Diseases

Mumps with Edema of the Chest. Joseph N. Rappaport, Illinois M. J. **83**:133 (Feb.) 1943.

The author reports 2 cases of mumps complicated with edema of the chest. Uneventful recoveries occurred.

Barbour, Peoria, Ill.

A Community Study of Carriers in Epidemic Poliomyelitis. Herbert A. Wenner and Albert E. Casey, J. Clin. Investigation **22**:117 (Jan.) 1943.

In an attempt to determine the distribution of poliomyelitis virus in the whole population at risk during a natural epidemic, stools of 176 of 181 persons in a defined community were examined in a postepidemic period. The virus was detected in the stools of 3 children from 2 to 6 years of age but in none of the stools of adults. The fact that only persons ill at the end of the epidemic provided virus-containing stools, though evidence of poliomyelitis was widespread in the group, indicated that the ease of detection of the virus diminishes in such a group with the decline of the epidemic.

Guest, Cincinnati.

Studies on Measles: IV. Results Following Inoculation of Children with Egg-Passage Measles Virus. Joseph Stokes Jr., Gerald C. O'Neil, Morris F. Shaffer, Geoffrey Rake and Elizabeth P. Maris, J. Pediat. **22**:1 (Jan.) 1943.

Two hundred and fifty-five children, for most of whom a fairly accurate history of never having had

measles was obtained, were inoculated with measles virus grown on the chorioallantois of chick embryos. The inoculations were made intranasally, intradermally and subcutaneously. The majority of the children, after an incubation period in many instances of only six or seven days, came down with a mild attack of measles with typical Koplik spots, conjunctivitis, rash, fever and coryza. None were very ill, and cough and malaise were minimal. Thus a very attenuated form of measles was produced. Further passage of the attenuated virus from some of these children to controls still resulted in a mild form of the disease, with no evidence that the virus regained virulence through human passage. No significant differences in reactions occurred with different inoculation methods, nor through two methods of preserving the virus, nor with different dilutions.

STETTENBENZ, Buffalo.

STUDIES ON MEASLES: V. THE RESULTS OF CHANCE AND PLANNED EXPOSURE TO UNMODIFIED MEASLES VIRUS IN CHILDREN PREVIOUSLY INOCULATED WITH EGG-PASSAGE MEASLES VIRUS. ELIZABETH P. MARIS, GEOFFREY RAKE, JOSEPH STOKES JR., MORRIS F. SHAFFER and GERALD C. O'NEIL, J. Pediat. **22**:17 (Jan.) 1943.

Children who had been previously inoculated with measles virus attenuated by growth on the chorioallantois of chick embryos and in whom a mild attack of measles had been produced were studied as to the results of (1) chance exposure to epidemic measles and (2) inoculation with injections of blood or intranasal inoculation with nasopharyngeal secretions from children with active measles.

The results were as follows: Of 22 children in the first group, 15 showed no evidence of disease, and 3 had typical measles, 1 mild measles and 3 extremely mild measles. Of 24 children in the second group, 13 showed no evidence of measles; 3 came down with typical measles, 2 with mild measles and 5 with an extremely mild infection, and 1 child had a nasopharyngitis. (Suitable control children and monkeys similarly inoculated had typical measles.) Thus, out of 46 children previously immunized with attenuated virus, only 6 had typical measles; 40 were completely or partially protected.

STETTENBENZ, Buffalo.

NONSPECIFIC THERAPY IN ANTERIOR POLIOMYELITIS: PRELIMINARY REPORT ON THE USE OF VITAMINS B AND E AND ARTIFICIAL FEVER. SIMON STONE, J. Pediat. **22**:142 (Feb.) 1943.

Stone treated groups of patients suffering from acute, subacute and chronic poliomyelitis with vitamins B and E and with artificial fever. In the acute stages, thiamine hydrochloride, injected intravenously or intramuscularly, was given in doses of 10 to 150 mg. daily. Vitamins B and E were administered concurrently, 12 to 24 cc. of vitamin B complex (Lederle) with 2 to 4 cc. of wheat germ oil (Lilly). Artificial fever treatments maintaining a temperature of 102 to 105 F. for one to three hours once or twice a week for several weeks were given to patients who still showed muscular tenderness and limitation of motion after the acute phase of the attack had passed. This was not given to patients with mild or nonparalytic poliomyelitis. No immobilization was carried out, except to prevent extreme relaxation of weakened muscles by means of sand bags or simple splints. Injections of thiamine hydrochloride were discontinued after the acute stage, but administration of the vitamin B complex and of vitamin E was continued through convalescence and in some instances for years. In 12 patients treated in the acute or subacute tender stage, 6 of whom received artificial fever, no deformities or contractures developed.

In the cases of chronic poliomyelitis, although definite results could not be estimated, there did appear to be improvement in muscular tone and there was increased well-being and better health.

The administration of the vitamins appeared to have a nonspecific beneficial effect in maintaining muscular tone and general well-being. Artificial fever therapy, well tolerated by all patients, reduced vasospasm, relieved muscular tenderness and improved circulation to the brain and spinal cord. Its combination with vitamins B and E brought rapid improvement in patients in whom progressive fibrositis was developing. The author is definitely convinced that the therapy outlined is a valuable adjunct in the treatment of poliomyelitis.

STETTENBENZ, Buffalo.

COLOSTRUM AS A SOURCE OF DIPHTHERIA ANTITOXIN IN ACTIVELY IMMUNIZED PREGNANT MOTHERS. JOSEPH LIEBLING and HERBERT E. SCHMITZ, J. Pediat. **22**:189 (Feb.) 1943.

The colostrum of nonimmunized mothers both with positive and with negative Schick reactions, contained no appreciable diphtheria antitoxin. Even after active immunization there was no rise in the antitoxin content in the colostrum of mothers with positive Schick reactions and but slight rise in that of mothers with negative reactions. There was no correlation with the antitoxin titer of the blood serum, which rose to high levels. These results tend to confirm the conclusions from other investigations that colostrum plays a minor role in the transfer of antitoxin to the infant.

STETTENBENZ, Buffalo.

THIAMIN EXCRETION TESTS IN CHILDREN WITH PARALYTIC POLIOMYELITIS. ROBERT WARD, ALBERT B. SABIN, VICTOR A. NAJJAR and L. EMMETT HOLT JR., Proc. Soc. Exper. Biol. & Med. **52**:5 (Jan.) 1943.

Seven children who had paralytic poliomyelitis were first given water and fruit juice for twelve to twenty-four hours shortly after coming to the hospital and then given 1 mg. of thiamine hydrochloride, and the amount of this vitamin excreted in the urine during the next four hours was determined. The results were similar to those obtained in previous studies on normal controls, which indicates that in paralytic poliomyelitis vitamin B_1 deficiency is not present. The authors plan to study other members of the vitamin B complex in relation to paralytic poliomyelitis. So far, however, no evidence of nicotinic acid deficiency has been found.

HANSEN, Minneapolis.

SUDDEN DEATH IN DIPHTHERIA. C. NEUBAUER, Brit. J. Child. Dis. **40**:3 (Jan.-March) 1943.

The case histories of 3 patients who died suddenly during the course of diphtheria are given.

Sudden death in diphtheria is due to one of three conditions: (1) gross myocarditis; (2) complete auriculoventricular block, and (3) paroxysmal ventricular tachycardia.

In the 3 cases described is illustrated the sequence of the pathologic changes prior to death due to the last two of these conditions.

LANGMANN, New York.

ACUTE ANTERIOR POLIOMYELITIS. C. J. McSWEENEY, Irish J. M. Sc., January 1943, p. 1.

This is a complete article on poliomyelitis. The history of the disease and its epidemiologic features are discussed. The virus enters probably by two routes, through the nose and through absorption from the bowel. The pathologic process involves edema of the cord, perivascular infiltration, and swelling and then death of the nerve cells. The cerebrospinal fluid shows increased pressure and the count of white blood cells, half of which are usually polymorphonuclears in the early stage of the disease and all of which are later lymphocytes. The globulin content is increased. The disease occurs largely in young children but has been observed in persons from 3 to 45 years of age. Carrier states are likely to result from subclinical forms of the disease. Multiple instances of the infection in the same family are rare but have been observed.

The disease occurs in the summer. The four stages of the clinical progress are as follows: (1) the preparalytic, lasting about three or four days; (2) the paralytic, up to ten days; (3) recovering up to the end of three months, and (4) the convalescent, up to two years. Signs of the disease are disinclination to flex the spine, hyperesthesia of muscles and head drop. There may be interference with reflex responses. Paralysis of the muscles sets in. The bulbar form of the disease interferes with circulation and respiration.

Differential diagnosis includes meningitis, acute and tuberculous encephalitis and peripheral neuritis. The prognosis in the majority of cases is good. The bulbar type of the disease is more frequently fatal.

There is no specific treatment. The author does not believe that the Kenny treatment is a panacea for poliomyelitis. He advocates prevention of contractures and protection of the legs at first, application of splints after three weeks and reeducation of the muscles. Prophylaxis consists in preventing congregation of people in public places, boiling and pasteurization of milk and water and protection from contamination by flies. Vaccines so far are of no use. Excreta must be thoroughly uncontaminated.

SNELLING, Toronto, Canada.

ORTHOPEDIC TREATMENT OF INFANTILE PARALYSIS. ARTHUR CHANCE, Irish J. M. Sc., January 1943, p. 13.

The author makes the following recommendations for the orthopedic treatment of infantile paralysis:

1. In the acute stage the patient should rest in a neutral position for ten days, with pillows, sand bags, foot blocks and supporting clothes. There should be passive movement of all joints daily without massage, exercises or electricity.

2. In the convalescent stage after the temperature drops splints should be used to prevent deformity and then passive movement is advised. Muscle records should be made. Heat should be applied to muscles, the infra-red lamp being useful. Massage and muscle reeducation by a competent masseuse are recommended. Hydrotherapy is valuable.

SNELLING, Toronto, Canada.

SURGICAL TREATMENT OF ANTERIOR POLIOMYELITIS. J. C. CHERRY, Irish J. M. Sc., January 1943, p. 21.

In a discussion of surgical treatment of anterior poliomyelitis the author advocates careful construction charts of muscles and the intelligent use of simple splints. Moreover, careful instructions should be given the parents when the child goes home from the hospital.

SNELLING, Toronto, Canada.

THE DYSENTERIES. W. L. CALOV, M. J. Australia **1**:155 (Feb. 20) 1943.

The author discusses the etiology, pathology, symptoms, diagnosis and treatment of protozoal (amebic, balantidial, giardial), and bacterial (Shiga, Flexner and Sonne) dysenteries. In the treatment of the acute stage of amebic dysentery, emetine is specific. It is given by hypodermic or intramuscular injection in a dose for adults of 1 grain (0.064 Gm.) a day for ten days. In order to eliminate the infection, the treatment with emetine should be followed in about a week by the administration of emetine bismuth iodide by mouth and chiniofon by bowel, in the manner recommended by Manson-Bahr. Recent investigations seem to prove that quinacrine hydrochloride is specific for giardial dysentery. Emetine is the drug of choice in the treatment of balantidial dysentery. Specific antidysenteric serums are of value only in the early stages of bacterial dysentery. Sulfapyridine or sulfaguanidine should be given in full doses for any severe bacterial dysentery.

GONCE, Madison, Wis.

MENINGOCOCCOSIS OF THE LOCOMOTOR APPARATUS. HELMUT W. JAEGER, Arch. Soc. cirujanos hosp. **12**:305 (Dec.) 1942.

Thirty-seven cases of meningococcic arthritis were found among 1,000 cases of meningococcic infection (3.7 per cent). The real frequency of arthritis is higher than this would indicate, for in postmortem examinations in 40 cases 9 instances of purulent synovitis not clinically diagnosed were found. This observation also indicates that meningococcemia may occur early in the disease, that is, that there may be simultaneous hematogenous invasion of the meningeal and extrameningeal tissues.

Two new types of the meningococcic infection in the locomotor apparatus are described, purulent bursitis and purulent tenosynovitis.

The term "meningococcosis" is proposed as a designation for the meningococcic infection on the whole, and inflammation of the joints, bursae and tendon sheaths is termed meningococcosis of the locomotor apparatus.

The anatomoclinical classification of Herrick and Parkhurst is questioned, and it is shown that in most cases the meningococcic arthritides are forms of purulent synovitis and that the so-called "meningococcic arthralgias" are also in reality arthritides.

The wrists and knees are the joints most frequently involved. Monoarticular and polyarticular involvements are observed with nearly the same frequency.

The prognosis is always good, but it is to be remembered that some cases have been reported in which meningococcic osteoarthritis led to ankylosis.

Unfortunately we have no adequate treatment for meningococcic arthritis; the sulfonamide drugs have no action on this type of infection. Although the prognosis is often good, a successful treatment is desirable for its economic importance. The period of hospitalization and the amount of medical attention required could then be reduced.

[FROM THE AUTHOR'S SUMMARY.]

THE KENNY METHOD IN THE TREATMENT OF ACUTE AND SUBACUTE POLIOMYELITIS. ALBERTO INCLÁN, Medica, Mantazas **3**:1 (Jan.-Feb.) 1943.

The author presents a short history of poliomyelitis in Cuba, including the treatments used. Then follows a complete résumé of the Kenny treatment, including the anatomic, and pathologic bases, and a critical analysis of the method. The actual treatment is described in detail. The author concludes that the results are definitely superior to those obtained by earlier methods, in the cases of acute and subacute poliomyelitis. He states the belief that surgical treatment may have only a limited use in reconstruction.

ZETTELMAN, Evanston, Ill.

THE RELATIONSHIP BETWEEN BENIGN LYMPHOCYTIC MENINGITIS AND POLIOMYELITIS. P. GAUTIER and G. HENNY, Confinia neurol. **4**:309, 1942.

Gautier and Henny note certain similarities between lymphocytic choriomeningitis and poliomyelitis, namely, in the constituents of the spinal fluid, in the epidemiology and in the clinical course. They state that the two conditions often occur simultaneously. They express the belief that all cases of lymphocytic meningitis which run a benign course should be regarded as instances of an attenuated form of poliomyelitis or of poliomyelitis in which the disease process is limited to the meninges.

DEJONG, Ann Arbor, Mich.
[ARCH. NEUROL. & PSYCHIAT.]

Acute Infectious Diseases

MODE OF ACTION OF GRAMICIDIN AND PENICILLIN IN THE TREATMENT OF INFECTIONS. CHARLES H. RAMMELKAMP, J. Bact. **45**:66 (Jan.) 1943.

Some of the characteristics of gramicidin and penicillin are described by the author. He states that these preparations are effective in vitro against gram-positive organisms. Gramacidin and tyrocidin are insoluble in body fluids and are toxic for all tissues. Therefore, according to the author, they should be used only for the treatment of localized infections. Penicillin, in contrast to gramicidin, is soluble in body fluids and is relatively nontoxic. It can be used in the treatment of generalized infections. Considerable difficulty is encountered when this is done, because penicillin is excreted rapidly in the urine and a significant amount is "destroyed" in the body. Parenteral administration of penicillin causes such poor diffusion that high concentration of the drug in the blood frequently cannot be obtained at the site of the infection. However, as soon as the concentration is sufficient an antibacterial effect is produced. Phagocytosis is not the cause of the action against the bacteria. Up to the present time nothing has been found in the body which inhibits the action of penicillin.

STOESSER, Minneapolis.

THE PREVENTION OF STREPTOCOCCAL UPPER RESPIRATORY INFECTIONS AND RHEUMATIC RECURRENCES IN RHEUMATIC CHILDREN BY THE PROPHYLACTIC USE OF SULFANILAMIDE. ANN G. KUTTNER and GERTRUDE REYERSBACH, J. Clin. Investigation **22**:77 (Jan.) 1943.

During two successive winters, 1940-1941 and 1941-1942, 108 rheumatic children were divided into two groups matched closely with regard to age, sex, number of previous rheumatic attacks and cardiac condition. From October to June in each period the children of one group were given small daily doses of sulfanilamide; the other children served as controls. During the first winter children weighing 75 pounds (34 Kg.) or less were given 1 Gm. daily in three divided doses, and children weighing 75 pounds or more received 1.3 to 2 Gm. daily. An average blood level of sulfanilamide of 2 mg. per hundred cubic centimeters was maintained. During the second winter the dose used was decreased to maintain an average blood level of 1.5 mg. per hundred cubic centimeters.

During the period from the fall of 1940 to the spring of 1942 not one of the children receiving the drug had rheumatic manifestations, whereas 14 of 30 in the control group who had streptococcus type 15 infections of the upper respiratory tract showed rheumatic relapses, and 4 additional children showed some evidence of reactivation of the rheumatic process. During 1941-1942 the ratio of incidence of streptococcic pharyngitis among the children in the control group and among those receiving sulfanilamide was 18 to 1, and the ratio for incidence of rheumatic recurrences in the two groups was 9 to 1. Toxic manifestations of sufficient severity to necessitate discontinuance of the use of the drug occurred in 15 per cent of the patients.

The effectiveness of sulfanilamide in preventing rheumatic recurrences was cited as evidence that infection with group A hemolytic streptococci is an important etiologic factor in rheumatic fever.

GUEST, Cincinnati.

EFFECT OF ORAL ADMINISTRATION OF SULFANILYLGUANIDINE ON EXPERIMENTAL BACILLARY DYSENTERY IN ISOLATED LOOPS OF COLON OF MACACA MULATTA AND EFFECT WHEN INTRODUCED INTO THE LOOPS. G. M. DACK and DOROTHY HOSKINS, J. Infect. Dis. **72**:11 (Jan.-Feb.) 1943.

Isolated segments of colon in 5 monkeys (Macaca mulatta) were inoculated with a strain of Bacterium dysenteriae (Flexner). An infection was produced in 2 monkeys by inoculation into isolated pouches composed of the cecum, the ascending colon and part of the transverse colon. Oral administration of 1 Gm. of sulfanilylguanidine daily for six days did not shorten the course of the disease in the 2 monkeys, although the organisms were not recovered after the drug was administered. In 3 monkeys inoculated in isolated segments of transverse colon, no dysentery was produced. One of these monkeys had loose stools intermittently over a period of two months after the experiments, and in one out of six trials Bact. dysenteriae was cultured. When sulfanilylguanidine was placed in the isolated segments of bowel there was a decrease in the number of gram-negative bacteria and an increase in the gram-positive organisms.

TOOMEY, Cleveland.

TOXOPLASMOSIS IN WILD RATS. THEODORE L. PERRIN, GEORGE D. BRIGHAM and EDGAR G. PICKENS, J. Infect. Dis. **72**:90 (Jan.-Feb.) 1943.

Spontaneous infection with Toxoplasma has been demonstrated in wild rats trapped in Savannah, Ga. The incidence of the infection in these rats, on the basis of this study, is 8 per cent.

TOOMEY, Cleveland.

PROTECTIVE ACTION OF VI BACTERIOPHAGE IN EBERTHELLA TYPHI INFECTIONS IN MICE. WALTER E. WARD, J. Infect. Dis. **72**:172 (March-April) 1943.

Mice were infected, by the use of the mucin technic, with strains of Eberthella typhi in the Vi phase. The blood was invaded within an hour after the injection. It was possible to protect more than 90 per cent of the

infected mice by intravenous treatment with specific bacteriophage instituted within four hours after infection. Nontreated mice and mice treated with nonspecific bacteriophage showed a mortality approaching 100 per cent.

Successive titrations of blood from the hearts of specifically treated animals showed an increase in the concentration of bacteriophage over a period of several hours, with traces present for more than sixty hours. Bacteriophage not active for the infecting strain of bacteria disappeared from the blood of infected mice in a few hours.

Treated mice were healthy carriers of the infecting organisms for about one month after infection. However, in many cases these organisms were in the degraded, or W, form. TOOMEY, Cleveland.

THE EFFECT OF SULFATHIAZOLE IN THE TREATMENT OF DYSENTERY IN CHILDREN. ELI RUBENS, MAX KAPLAN, MAXWELL P. BOROVSKY and MAURICE L. BLATT, J. Pediat. **22**:70 (Jan.) 1943.

Sulfathiazole was found to have a definite value in the treatment of dysentery in a group of children studied by the authors. It was of interest that patients whose stool cultures yielded Bacterium dysenteriae responded better than patients who had clinically similar diarrhea but from whose stools Bact. dysenteriae could not be recovered. Use of the drug was started two to four days after the patients' admission to the hospital and continued until the stools became normal in consistency, color and number and until three successive stool cultures were negative. The usual dose of sulfathiazole was 1.5 Gm. per pound of body weight in twenty-four hours. In addition, supportive therapeutic measures, such as parenteral administration of fluids and transfusions, were used, depending on the child's condition. The number of days of diarrhea after sulfathiazole therapy was started ranged from two and nine tenths to four and seven tenths, as compared with eleven and five-tenths total (eight and eight-tenths) days of divergent therapy for the control group. No deaths occurred in the entire series of 46 cases.

STETTENBENZ, Buffalo.

PROPHYLACTIC USE OF SULFANYLGUANIDINE IN A DYSENTERY OUTBREAK. PASCAL F. LUCCHESI and NATHANIEL GILDERSLEEVE, J. Pediat. **22**:319 (March) 1943.

Sulfanylguanidine (sulfaguanidine) was found to control effectively the spread of bacillary dysentery which had broken out in a group of 118 ward patients. Of 45 exposed persons given the drug, dysentery developed in none. Forty-eight who were exposed less were not given the drug, and dysentery developed in 4 of these. Twenty-nine children who had come down with the disease recovered promptly after administration of the drug, and there were no toxic effects.

STETTENBENZ, Buffalo.

TWO CASES OF TYPHOID FEVER TREATED WITH SULFAGUANIDINE. D. D. ALTHOUSE and MARY KIRKWOOD, New York State J. Med. **43**:450 (March 1) 1943.

Two children, 11 and 13 years of age, who had typhoid were treated with sulfaguanidine. The drug had no effect on the temperature, but it shortened the duration of the disease and reduced the abdominal distention and tenderness. AIKMAN, Rochester, N. Y.

ARTIFICIAL FEVER THERAPY IN BRUCELLOSIS. GENEVIEVE L. JOY and FRED B. MOORE, Brit. J. Phys. Med. **6**:36 (March-April) 1943.

Eighteen patients with acute and chronic brucellosis were treated with artificial fever. A high humidity fever cabinet was used. In 13 of the 18 cases, or 72.2 per cent, there were clinical remissions. In 5, or 83.3 per cent, of the 6 cases of acute brucellosis and in 8, or 66.6 per cent, of the 12 cases of the chronic disease there were favorable results.

HARTMAN, Portsmouth, Va.

OBSERVATIONS ON FLEXNER DYSENTERY. W. ALEX CALDWELL and S. W. HARDWICK, Edinburgh M. J. **50**:129 (March) 1943.

The writers discuss an outbreak of dysentery among adults in a hospital due to the introduction of 50 patients evacuated from a hospital for persons with mental disease after an air raid. They cite other instances in which epidemics came from proved carriers. An improved technic for collecting fecal specimens is described. It was found that the desoxycholate-citrate medium of Hynes gave better growth than the MacConkey medium. The writers believe that the general practitioner would be able to be of more service if he had adequate laboratory facilities for testing for the presence of Flexner and Sonne types of dysentery bacilli. Vaccine as a prophylactic was disappointing. Sulfaguanidine appears to be effective in the treatment of the disease. NEFF, Kansas City, Mo.

STUDIES ON AIR-BORNE VIRUS INFECTIONS. D. B. EDWARD, W. J. ELFORD and P. P. LAIDLAW, J. Hyg. **43**:1 (Jan.) 1943.

Virus infections are prominent in any list of air-borne diseases. Past influenzal pandemics and present war conditions prompted a review of the literature on experimental spread of this disease as well as further experiments.

In ferrets, it has been shown that the disease can be produced not only by inhalation of the virus but by its entrance through the eye. The infectivity of the organism, outside the body, in the air, does not persist more than an hour. Ultraviolet radiation seems to destroy it. In this experiment, mice were regularly infected by spraying the virus in the air. Bright daylight increased the rate at which spray organisms died off in the air.

JANNEY, Wauwatosa, Wis.

STUDIES ON AIR-BORNE VIRUS INFECTIONS. D. G. EDWARD, DORA LUSH and R. B. BOURDILLON, J. Hyg. **43**:11 (Jan.) 1943.

The use of ultraviolet radiation for disinfecting air appears likely to become of considerable practical importance. It has been shown of value in reducing cross infection in children's hospitals, schools and operating theaters. Mumps, measles and chickenpox are among the infections whose spread appears to be diminished by its use.

Experiments conducted by the authors showed that rapid and effective sterilization of atmospheres containing influenza or vaccinia virus, and probably also herpes simplex virus, can be obtained by ultraviolet radiation of wavelength 2,537 angstrom units. At least 99 per cent, and probably more, of an aerosol of influenza virus was killed by exposure for six seconds at a distance of 2 cm., with either a Hanovia or a General Electric

Company "Sterilamp." The same effect was found for vaccinia virus. With herpes the result was similar but somewhat less satisfactory.

JANNEY, Wauwatosa, Wis.

FURTHER OBSERVATIONS ON ACUTE STAPHYLOCOCCAL INFECTION. E. C. B. BUTLER and F. C. O. VALENTINE, Lancet **1**:194 (Feb. 13) 1943.

The chief objects of this paper on severe staphylococcic infections are to demonstrate the value of repeated quantitative blood cultures, to emphasize the importance of the primary lesion as a continuing source of infection of the blood and to discuss the merits of antitoxin and chemotherapy.

Special attention must be paid to combating the bacteremia, since nearly all the deaths from staphylococcic infections are due to bacteremia and its sequelae.

Excision or drainage of the probable primary focus, especially if it is of considerable standing without regard to its apparent insignificance, may be the most important single item in treatment.

Sulfathiazole seemed to have more influence on the staphylococcus than the other sulfonamide compounds, but in the authors' experience its effect on bacteremia is slight. However, it seemed to benefit those with metastatic lesions, particularly when the lungs were involved.

To patients with severe toxemia it seems logical to give antitoxin in the early stages of bacteremia when it can be shown or presumed that the titer of antileukocidin in the serum is low and toxemia may be expected to exist.

LANGMANN, New York.

THE PLACE OF QUININE IN THE TREATMENT OF SUBTERTIAN MALARIA. A. D. CUST, M. J. Australia **1**:119 (Feb. 6) 1943.

Cust's experience indicates that quinine may be employed in the treatment of subtertian infections with safety if the patient has taken reasonable care to protect himself against malaria, that is, if the weight and frequency of infections have been reduced. When no reasonable prophylaxis has been employed, through carelessness, ignorance or lack of opportunity, the ingestion of quinine may prove dangerous in precipitating blackwater fever in patients suffering from subtertian malaria. In these circumstances it is considered advisable to replace quinine by an antimalarial drug of the type of quinacrine hydrochloride.

GONCE, Madison, Wis.

Chronic Infectious Diseases

DISAPPEARANCE OF TUBERCULIN REACTION IN CHILDREN UNDER TREATMENT FOR ALLERGIES. F. M. POTTENGER JR. and F. M. POTTENGER, Am. Rev. Tuberc. **47**:11 (Jan.) 1943.

After primary localized tuberculous infection, bacillary products escape into the blood stream and produce sensitization of the tissues of the body to the bacilli and their proteins, with subsequent increased resistance. The inflammatory portion of this protective reaction is called allergy. Tissue cells once rendered allergic are likely to remain permanently so. However, lessening or disappearance of allergy under certain circumstances does not seem to be sufficiently recognized. In 41 children whose cases are reported in this paper, reactions to tuberculin (first dose purified protein derivative) changed from positive to negative while the children were undergoing treatment for conditions other than tuberculosis. Most of them were being treated for bronchial asthma, hay fever or chronic bronchitis. All patients were put on a diet rich in protein and animal fat and relatively low in carbohydrate. Muscle meat and organs were used in a proportion of about 1:3. Vitamins were for the most part obtained from natural foods. Rice, molasses, malt and sometimes cod liver oil were used as supplemental sources of vitamins. The proportions of protein, fat and carbohydrate were roughly 1-1-1. In addition each child was given a potent extract made from adrenal cortex.

Tissue permeability has been shown to be an important factor in allergic diseases. There is evidence to suggest that nutrition may play a part in the permeability of tissue and in resistance to infection. It would appear that among the important factors responsible for the change in the allergic response of these children to the purified protein derivative of tuberculin were the diet high in protein and fat and natural sources of vitamins and low in carbohydrate and the administration of a potent extract of adrenal cortex which is known to have a marked effect on tissue permeability.

EUGENE SMITH, Ogden, Utah.

COMBATING TUBERCULOSIS IN UNION OF SOCIALIST SOVIET REPUBLICS. F. LEVITIN, Am. Rev. Tuberc. **47**:121 (Feb.) 1943.

Some idea of the progress made in combating tuberculosis in modern Russia may be had from a consideration of the increase in the number of dispensaries for persons having tuberculosis from 42 under the old regimen to 1,408 under the new, and of beds in hospitals and sanatoriums for patients with tuberculosis from 307 to 53,523 at the beginning of the present war, of which 30,857 are allocated to children. The specific tuberculosis program is tied in closely with the general health program and with general hospital and polyclinic medical service.

Antituberculosis measures have been developed in cooperation with workers and trade unions. A special feature has been the organization of artels (workmen's associations) in which the patient is given graduated labor in the manufacture of various wares, together with a reduced working day and proper nutrition. Night sanatoriums have been organized to provide patients with necessary treatment and nutrition without their having to discontinue their work. Due to these and other measures, the greatest decrease in the incidence of tuberculosis has been achieved among industrial workers.

SMITH, Ogden, Utah.

THE EFFECT OF SULFANILAMIDE ON EXPERIMENTAL LEPROSY. CECIL KRAKOWER, PABLO MORALES-OTERO and JOSEPH H. AXTMAYER, J. Infect. Dis. **72**:1 (Jan.-Feb.) 1943.

One per cent sulfanilamide fed to rats and mice infected with the mouse strain of lepra bacillus throughout the whole of the experimental period completely inhibited the growth and development of the leproma at the site of inoculation and prevented the occurrence of distant metastases.

One per cent sulfanilamide and, in a single trial, 1 per cent sulfathiazole were found to arrest the further development of the leproma and its metastases when given after an untreated period of the infection.

One per cent sulfanilamide given during the first part of the infection and then withdrawn permitted the inhibited lepromatous lesion to evolve again, but at a slower rate than would be expected. The probable reasons for this have been given.

There is no indication, however, that, with inhibition of the lesion produced by the chemotherapeutic agent, the lepra bacilli are killed in any appreciable numbers. In view of this and in the absence of any clear evidence that the bacilli, alive or dead, can be digested by the cells of the host, the permanency and unaltered character of the inhibited lesion are understandable, as is its unfailing progression following removal of the inhibiting agent. TOOMEY, Cleveland.

OBSTRUCTIVE EMPHYSEMA AND ATELECTASIS IN TUBERCULOSIS OF INFANTS AND CHILDREN. JULIO MENEGHELLO and CLEMENT A. SMITH, J. Pediat. **22**:265 (March) 1943.

Meneghello and Smith present the case histories of 15 children with tuberculosis, in 9 of whom partial or complete bronchial occlusion developed, resulting in atelectasis or in obstructive emphysema. Nine of the 15 children were under the age of 2 years, and the soft, easily compressible bronchus of the infant was a definite factor. Symptoms were usually insidious and rather indefinite, but one is impressed by the frequent mention of a wheezing type of respiration. Bronchoscopy is indicated in such cases as a diagnostic measure and to determine whether the obstruction is due to pressure from outside the bronchus or from within, as by a mass of granulation tissue. One child whose case is described had an almond embedded in a mass of tuberculous granulation tissue. The prognosis is good for the majority of such patients, even though the atelectasis or emphysema may persist for six months.

STETTENBENZ, Buffalo.

CONTROL OF TUBERCULOSIS IN CHILDREN BY PREVENTION OF ITS SPREAD THROUGH CONTACT. WILLIAM J. ORR, New York State J. Med. **43**:152 (Jan. 15) 1943.

Little has been done to protect students from teachers with active tuberculosis. Only twenty states have laws requiring yearly physical examinations of teachers. Educational programs popularizing the examination of teachers will lead to the more general enactment of compulsory regulations. Cooks, waiters, food handlers and domestic servants should also be examined at regular intervals. AIKMAN, Rochester, N. Y.

CORRELATION OF EXTENT OF TUBERCULOSIS WITH AMOUNT OF POLYSACCHARIDE IN THE SERUM. FLORENCE B. SEIBERT, J. WALTER NELSON and MABEL V. SEIBERT, Proc. Soc. Exper. Biol. & Med. **52**:219 (March) 1943.

The polysaccharide content of the serum of patients in various stages of tuberculosis was found to be increased in proportion to the extent of the disease. This increase could not be correlated with an increase in the total protein content of the serum.

HANSEN, Minneapolis.

UNRECOGNIZED CONGENITAL SYPHILIS. DAVID NABARRO, Lancet **1**:291 (March 6) 1943.

The belief is prevalent in the medical profession, and most students are being taught, that congenital syphilis is a rare disease today. This mistaken conviction stems from the fact that the congenital syphilis seen today is different from that seen fifty or even twenty-five years ago. It is exceptional, or it was until the outbreak of the present war, to see a frank case of the infantile disease with rash, snuffles and epiphysitis and with the "old man" appearance which still figures in the textbooks. Instead there may be only an evanescent rash, possibly accompanied by slight snuffles and usually attributed to catarrh or infection of the adenoids.

It is impossible to give even an approximate figure of the number of patients suffering from congenital syphilis. The British Social Hygiene Council estimated that of the 25,000 stillbirths in Great Britain per year 4,000 were due to syphilis. This figure is an index of the considerable number who survive and become a prey of syphilitic manifestations.

During the six years from 1917 to 1922 inclusive, the author saw at Great Ormond Street 322 new patients with congenital syphilis, of whom 58 died under 2 years of age, whereas during the six years from 1933 to 1938 inclusive he saw 123 new patients at Great Ormond Street and 73 more at two other institutions. These figures are evidence of a considerable decline, but they are still far too high. With the serious increase in the number of new cases of venereal disease in adult patients reported during the past two years there is bound to be a corresponding increase in the number of persons with congenital syphilis unless adequate precautions are taken.

The author makes a fervent plea for blood tests of all expectant mothers and adequate treatment of those having positive reactions in such tests.

LANGMANN, New York.

COMPARATIVE STUDIES OF TUBERCULOUS INFECTION IN CHILDREN IN VARIOUS DISTRICTS OF THE CAPITAL. JOAQUIN ENRIQUE HERRAN, Rev. de hig. y med. esc. **2**:34, 1943.

A comparative study was made of tuberculosis infection in groups of school children belonging to different quarters of Buenos Aires. The groups correspond to the nine open air schools of the national board of education.

The reaction to tuberculin was positive in 29.52 per cent of 2,304 school children, whose average age was 8.559 years.

The comparative statistical study showed that schools 1 and 4, the first in Lezama Park and the second in the Chacarita quarter, had a higher than average index of positivity, and school 6, in Villa Devoto, had an incidence lower than the average for the whole city.

[FROM THE AUTHOR'S SUMMARY.]

Diseases of Blood, Heart and Blood Vessels and Spleen

THE INCIDENCE OF RHEUMATIC STIGMAS IN HEARTS WHICH ARE USUALLY CONSIDERED NONRHEUMATIC. E. M. HALL and L. R. ANDERSON, Am. Heart J. **25**:64 (Jan.) 1943.

A microscopic study was made of 112 hearts which were free of rheumatic valvular lesions as commonly understood. Arteritis, fibrinoid changes, elastic tissue alterations, Aschoff bodies and histiocytes were found frequently. About 90 per cent of the hearts studied revealed stigmas of rheumatic infection in the myocardium.

The authors believe their study indicates a widespread distribution of the rheumatic virus, comparable perhaps to the distribution of the organisms causing tuberculosis and poliomyelitis; moreover, their opinion is that the greater percentage of the population is immune to the virus of rheumatic fever. GIBSON, Chicago.

PATENCY OF THE DUCTUS ARTERIOSUS IN ADULTS. A. KEYS and M. J. SHAPIRO, Am. Heart J. **25**:158 (Feb.) 1943.

The authors studied simple, typical patency of the ductus arteriosus in 57 adult patients. In over 40 per cent of the persons death was due to subacute bacterial endarteritis, and in 28 per cent, to congestive heart failure. For those over 17 years of age, life expectancy was only about twenty-five years, or approximately half that of the general population.

The authors believe that an attempt at ligation of the ductus is justifiable even in the absence of signs of decreasing adjustment to the defect. They point out, however, that in adults conditions which make operation difficult or impossible will frequently be present.

GIBSON, Chicago.

THE RESULTS OF SURGICAL TREATMENT OF PATENCY OF THE DUCTUS ARTERIOSUS COMPLICATED BY SUBACUTE BACTERIAL ENDARTERITIS. A. S. W. TOUROFF, Am. Heart J. **25**:187 (Feb.) 1943.

Eleven patients with patency of the ductus arteriosus complicated by endarteritis due to Streptococcus viridans and 1 with patency complicated by endarteritis caused by Staphylococcus aureus submitted to ligation (10 cases) or division (2 cases) of the ductus. Two patients died of operative hemorrhage. Seven were cured. Three failed to recover from the infection. Of these 3 patients, 2 presented evidence of vegetations on the valves of the heart prior to operation. Surgical treatment should be undertaken as soon as the diagnosis has been established.

GIBSON, Chicago.

STUDIES ON EXPERIMENTAL AND CLINICAL HYPOCHLOREMIA IN MAN. JOSEPH B. KIRSNER, WALTER LINCOLN PALMER and KATHRYN KNOWLTON, J. Clin. Investigation **22**:95 (Jan.) 1943.

In 2 adult men with pyloric obstruction secondary to duodenal ulcer, deprivation of chloride was produced slowly by Wangensteen aspiration of the gastric contents while 3,000 to 4,500 cc. of 5 per cent dextrose in distilled water was administered intravenously. A state of severe alkalosis resulted, but without marked retention of nitrogen or decrease in renal function as measured by urea clearance. The histamine-stimulated gastric secretion remained normal.

GUEST, Cincinnati.

AN IMPROVED METHOD FOR DETERMINING THE SEDIMENTATION RATE OF THE RED BLOOD CORPUSCLES. F. RAPPAPORT, J. Lab. & Clin. Med. **28**:746 (March) 1943.

The sedimentation rate varies with the external temperature, being accelerated by heat and retarded by cold. In order to exclude this source of error, an apparatus was constructed which employs a wide-necked thermos flask filled with water at 20 C. Blood is taken from the finger tip, with a pipet.

WILKINSON, Galveston, Texas.

CHRONIC HEMOLYTIC ANEMIA WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (MARCHIAFAVA-MICHELI SYNDROME): REPORT OF A CASE WITH MARKED THROMBOCYTOPENIA IN A FIVE-YEAR OLD CHILD. PAUL P. PIERCE and C. ANDERSON ALDRICH, J. Pediat. **22**:30 (Jan.) 1943.

A case of chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria is reported by Pierce and Aldrich. The patient was a child of 5 years, the youngest reported in the literature. The onset was sudden, manifested by severe abdominal pain and subsequent appearance of icterus, purpura and palpable spleen. Studies of the blood showed an unusually low platelet count and evidence of severe hemolytic anemia. Nocturnal hemoglobinuria was present. This symptom was at first overlooked, and it was thought that the patient had idiopathic thrombopenic purpura. Splenectomy was performed, which elevated the platelet count and relieved the purpura; however, the hemolytic anemia and paroxysmal hemoglobinuria were unaffected. The patient at present is well, although the red blood cell count averages 1,000,000 to 3,000,000 per cubic millimeter. Hemoglobinuria occurs two or three times a month and is usually associated with an infection of the respiratory tract.

Ordinarily splenectomy is contraindicated in these cases, because of the resulting high mortality. Transfusion and infections may produce hemoglobinuria. The treatment is the removal of foci of infection and the administration of an adequate diet, with iron to combat the anemia.

STETTENBENZ, Buffalo.

THE DIAGNOSIS AND EVALUATION OF COMPENSATED AND UNCOMPENSATED PATENCY OF THE DUCTUS ARTERIOSUS. JOHN P. HUBBARD, J. Pediat. **22**:50 (Jan.) 1943.

Hubbard describes the features of patent ductus arteriosus, both compensated and uncompensated.

Patients with the compensated type have a small arteriovenous shunt with no effect on the peripheral circulation or the cardiac reserve. Diagnosis is readily made by the typical crescendo systolic bruit extending into diastole and then decreasing in intensity. The murmur is loudest in the second left interspace over the pulmonic area.

In patients in whom the patency is uncompensated a large arteriovenous shunt exists and there is evidence of circulatory failure. Characteristically, there are a low diastolic pressure and other evidences of aortic insufficiency. The heart is enlarged, and there is pulmonary congestion, best observed by roentgen examination of the chest. In children, growth and development are impaired. To date, Hubbard believes that surgical ligation of the duct should be reserved for the cases in this group. The operation should be performed as soon as circulatory embarrassment ensues, regardless of age. The case of an infant is cited for whom the diagnosis of patent ductus arteriosus was made at the age of 5 months. Congestive failure was already present. Successful surgical ligation of the duct was performed when the child was 11 months old.

STETTENBENZ, Buffalo.

ENUMERATION AND DIFFERENTIATION OF LEUKOCYTES IN THE COUNTING CHAMBER WITH PROPYLENE GLYCOL-AQUEOUS STAINS. THERON G. RANDOLPH, with the technical assistance of ELIZABETH B. GIBSON, Proc. Soc. Exper. Biol. & Med. **52**:20 (Jan.) 1943.

The hemolytic and solvent properties of propylene glycol suggested its use as a diluent for blood for leukocyte counts. The author used a mixture of equal parts of solution I (methylene blue, 0.1 Gm., and propylene glycol, 100 cc.) and solution II (eosin B, 0.1 Gm., and distilled water, 100 cc.) as a diluent; he was able to make accurate total leukocyte counts and in addition to make differential white cell counts directly in the counting chamber.

HANSEN, Minneapolis.

DISCUSSION ON NUTRITIONAL ANEMIA IN CHILDREN AND WOMEN: A WARTIME PROBLEM. HELEN M. M. MACKAY, LUCY WILLS, R. H. DOBBS and K. BINGHAM, Proc. Roy. Soc. Med. **36**:69 (Dec.) 1942.

From this discussion on nutritional anemia in children and in women in wartime the following conclusions were drawn:

1. The blood picture is not a true reflection of the state of health of the child. A well developed child has often lower hemoglobin and red blood cell values than a less well developed child.

2. The blood picture is not necessarily an index of the iron content of the diet.

3. Iron administered considerably in excess of the body's requirements causes as a rule no change in the hemoglobin level of the normal child. Occasionally there may ensue immediately after its presentation a slight, but only transient, rise in the hemoglobin level.

4. Iron administered in medicinal doses to persons with hypochromic anemia causes a considerable rise in the level of hemoglobin. The maximum rise, however, is not sustained but falls after several weeks to a more moderate and normal level, although the same or even a larger intake of the drug is continued.

5. Iron in medicinal doses would thus seem to exert a stimulating or irritant effect on the hemopoietic tissues as well as to supply material essential for hemoglobin formation. Otherwise, the highest level produced would be maintained. This stimulating effect is more evident in the abnormal than in the normal state.

6. The maximum level to which the hemoglobin can be raised by the administration of iron cannot be considered the optimum or physiologic level, since the highest values induced are not maintained.

7. The individual optimum level of hemoglobin varies with age and sex. This seems to be lower in infants than in older children, in children than in adults, and in female than in male patients.

8. The individual optimum level of hemoglobin is also affected by factors which influence the oxygen supply or needs of the tissues, such as environment, defects in the cardiovascular system and abnormalities of metabolism.

9. The term nutritional anemia seems to be too loosely employed. It is unjustifiable to speak of a low hemoglobin level as presumably arising from a dietary error. Many factors determine the hemoglobin level of a person, all of which must be considered before the true cause can be assigned.

WILLIAMSON, New Orleans.

PATENT DUCTUS ARTERIOSUS COMPLICATED BY SUBACUTTE BACTERIAL ENDARTERITIS TREATED BY LIGATURE OF THE DUCTUS. OSWALD W. TUBBS, Proc. Roy. Soc. Med. **36**:175 (Feb.) 1943.

Patent ductus arteriosus complicated by subacute bacterial endarteritis occurred in a woman 22 years of age. During childhood her activities were normal, and there was no cyanosis. She was well until five months earlier when she had three teeth extracted, after which she felt weak but returned to work. One month later she became sick again, with pain in the right side, shortness of breath and fever varying from 99 to 103 F. She was told at the time that she was suffering from valvular disease of the heart. Subsequently she had three attacks of pleuritic pain in the right side of her chest. She was then admitted to the hospital. Details of the physical examination and the medical and surgical treatment are all given fully in the report.

WILLIAMSON, New Orleans.

THE SEDIMENTATION RATE IN SCHOOL CHILDREN OF THE FEDERAL CAPITAL. JOAQUIN ENRIQUE HERRAN and CIRO T. BIETTI, Rev. de hig. y med. esc. **2**:25, 1943.

A study was made of the erythrocyte sedimentation rate in 190 school children, 144 of whom were clinically and roentgenographically normal and had negative reactions to the Mantoux test with dilutions of 1:1,000 and 1:100 and 46 of whom were clinically and roentgenographically normal but had positive Mantoux reactions.

In the first group the average rate of sedimentation was 6.70 mm. in the first hour for the girls, with an average age of 9.83 years, and 6.56 mm. for the boys, with an average age of 9.03 years. The average rate for all of the children of this group was 6.62 mm. in the first hour, and the average age was 9.40 years.

In the second group the average rate of sedimentation was 7.27 mm. for boys (8.76 years) and 8 mm. for girls (10.20 years); the average rate for this whole group was 7.69 mm. in the first hour, and the average age was 9.54 years. The average for the allergic group was slightly higher than the average for the normal group.

The results obtained for the 190 children, considered as a whole, give an average sedimentation rate of 6.70 mm. for boys, with an average age of 9 years (9.03), and 7.07 mm. for girls, with an average age of 10 years (9.99). The total average for boys and girls together is 6.88 mm., with an average age of 9.50 years. Ninety per cent of the children had sedimentation rates between 2 and 15 mm. in the first hour, and 78.95 per cent between 2 and 11 mm.

[FROM THE AUTHORS' SUMMARY.]

Diseases of Nose, Throat and Ear

THE SULFONAMIDE DRUGS IN THE TREATMENT OF ACUTE OTITIS MEDIA. HAROLD G. TOBEY, Ann. Otol., Rhin. & Laryng. **51**:945 (Dec.) 1942.

Tobey discusses six concepts which have been definitely established with regard to sulfonamide compounds: 1. They are free to act on infection wherever they can be carried by the blood stream and they will not act where the vessels are blocked by thrombosis, as in the proximity of a localized abscess. 2. The presence or the absence of antibacterial antibodies is important. 3. The toxicity of the drugs is well known and shows most often between the tenth and the fourteenth day of administration. 4. About 10 to 15 per cent of patients become sensitized to the sulfonamide compound. If the preliminary medication has failed to stop the spread of the infection, the readministration of the drug, in order to combat any complication which may have arisen later, can cause alarming symptoms. 5. There is a tendency for sulfonamide therapy to mask symptoms in otitis media and mastoiditis. 6. There is a definite but small percentage of deaths connected with the use of sulfanilamide and sulfapyridine.

Otitis media is distinctly seasonal, 75 per cent of the cases occurring, according to Page, in the winter and spring and 25 per cent in the summer and fall. The severity depends on the virulence of the organism which predominates in the prevailing epidemic. The epidemics of infection of the upper respiratory tract vary greatly

in their predilection for the middle ear, and there is wide variation in the infecting organisms.

If chemotherapy is going to be successful, there will be a pronounced change for the better within forty-eight to seventy-two hours, and Tobey suggests that, if it is to be tried, the patient should be hospitalized if possible, and confined to bed. The dosage of sulfadiazine must be adequate to obtain a blood level of at least 10 mg. per hundred cubic centimeters of blood. This will depend on the patient's capacity to sustain a satisfactory blood level. The author feels that there should be an arbitrary time limit of seventy-two hours. By this time the cultures made at the time of paracentesis will have been reported on. If the progress is satisfactory, the administration of the drug may be omitted or continued at the same or a reduced dose for a period not exceeding ten days. If the progress is not satisfactory, sulfanilamide for the streptococcus, sulfapyridine or sulfathiazole for the pneumococcus or sulfathiazole for the staphylococcus should be substituted for the sulfadiazine. The continuance of a purulent discharge from the ear, after a week of what is considered adequate chemotherapy from the beginning, should be evidence that the infection has not been controlled, and continuation of the drug therapy presents grave responsibilities in regard to toxemia, sensitization to the drug and masking of symptoms.

MILLER, Philadelphia. [ARCH. OTOLARYNG.]

SULFATHIAZOLE IN MASTOIDECTOMY WOUNDS. WILBER D. CURRIER, Ann. Otol., Rhin. & Laryng. **51**:955 (Dec.) 1942.

Currier briefly reviews the literature on the use of sulfonamide compounds in mastoidectomy wounds and reports the results in 84 in which sulfathiazole was used. The solubility of sulfathiazole in tissue fluids is only 150 mg. per hundred cubic centimeters, but this is ten to fifteen times greater concentration than can be obtained by oral administration. As the pathologic process of mastoiditis usually walls off the infection, the absorption is small and the local therapeutic effect is great, and there is no danger of too high a blood concentration from the local use. Currier, as well as others, has been unable to detect sulfathiazole in the blood when the drug was used in mastoidectomy wounds. Currier's investigations have made him decide that sulfathiazole is the drug of choice and that its use in a snugly closed mastoidectomy wound without drain, accelerates healing, decreases postoperative drainage and lessens postoperative hospitalization.

MILLER, Philadelphia. [ARCH. OTOLARYNG.]

EARACHE: THE COMMON CAUSES AND PROBABLE NERVE PATHWAYS. E. EDWARD TREMBLE, Ann. Otol., Rhin. & Laryng. **51**:1017 (Dec.) 1942.

Sensation is supplied to the anterior walls of the external auditory canal and a small part of the anterior portion of the auricle by the auriculotemporal branch of the third division of the fifth nerve. Practically the whole surface of the auricle is supplied by the auricular branches of the great auricular and small occipital nerves from the second and third cervical segments, with an occasional twig from the great occipital nerve. Arnold's nerve, the auricular branch of the vagus, supplies the posterior and inferior walls of the external canal and the concha. There is some evidence that the seventh nerve supplies some sensation to the concha and to the posterior surface of the auricle, and the geniculate ganglion appears to have a part in innervating the concha and the external canal.

The tympanic membrane is supplied in its posterior portion by Arnold's nerve and in the anterior portion by the auriculotemporal nerve. The inner surface receives sensation through the tympanic nerve, a branch of the ninth.

The middle ear is supplied with sensation through a plexus on the inner wall formed by nerves derived from Jacobson's nerve from the ninth nerve, the geniculate ganglion of the facial nerve and the caroticotympanic branches from the carotid sympathetic plexus. The mastoid cells are supplied sensation through a mastoid branch of the tympanic plexus, and the skin of the mastoid is innervated by branches of the great auricular and small occipital nerves.

Earache may be due to a condition in the external canal, the middle ear or the mastoid cells or it may be due to a more remote cause. Sinusitis, particularly sphenoethmoid sinusitis, may produce otalgia through the sphenopalatine ganglion, along the superficial petrosal nerve to the geniculate ganglion, which sends branches to the tympanic plexus. Dental involvement, particularly of the lower jaw, causes more than half of the otalgias from remote causes. The pain is steady, persistent and worse at night and is carried through branches of the fifth nerve. Dental caries is the most common cause, but occasionally an unerupted wisdom tooth may cause pain.

Lesions of the side of the tongue, particularly of the anterior two thirds, caries of the lower teeth, inflammation of the salivary glands and disease of the temporomandibular joint may all cause reflex pain through the auricular branch of the auriculotemporal nerve. A lesion on the anterior part of the tongue may cause pain in front of the ear through involvement of the nerve endings of the auriculotemporal nerve through the lingual branch of the fifth nerve. A lesion on the posterior third may cause severe pain within the ear through irritation of the ninth nerve with reflex pain through its tympanic branch to the tympanic plexus.

Ulcerative lesions of the larynx or the upper part of the trachea may cause reflex otalgia through irritation of the superior laryngeal branch of the tenth nerve.

MILLER, Philadelphia. [ARCH. OTOLARYNG.]

SPEECH DISORDERS AND THEIR TREATMENT. STANLEY COBB, Bull. New York Acad. Med. **19**:34 (Jan.) 1943.

Unlike other vertebrates, which specialize and reach narrow superiority by unique development of one type of sense organ, man depends on a leading hemisphere evenly developed in the reception and the elaboration of all types of sensory impression. Language is a product of this phenomenon and is made possible through it.

In the central nervous system of man speech is integrated at five important levels. These are not exact and there may be overlapping, but the division is significant enough for practical purposes.

Level I is represented by the neuron, from a nucleus in the medulla (seventh, tenth or twelfth) to a peripheral organ of speech—lips, tongue or larynx. Through this level all nerve impulses concerned with speech must pass.

Level II is the neuron arising from the motor cortex and ending in the medulla around the bulbar nuclei, its fibers passing down the corona radiata and through the internal capsule to the peduncles and the medulla. This, too, is a common pathway for all complex speech integrations of the higher levels.

Level III runs up from the medulla to the cerebellar cortex, then to the cerebellar efferent nuclei and upward to the midbrain, the thalamus and the motor cortex. Thus is supplied the mechanism of coordination necessary to the control of speech. These three levels may be considered together as a motor mechanism.

Level IV is in the Broca area. It involves symbolization and meaning. This is the "leading hemisphere," usually on the left.

Level V is the most highly integrated. It is associated with the great association area of the frontal and the parietal lobes. It involves memories, individual life experiences, impact of one person on another and emotional and social reactions influenced by all factors which make up the character and the personality of the individual.

The author presents a practical working explanation of the functional result of damage, physical or psychologic, to these particular levels. The various types of dysphasia and aphasia are discussed, with clinical emphasis on their significance, and the mode of therapy suitable to each syndrome. The article is well illustrated.

JAHR, Omaha.

STREPTOCOCCUS SALIVARIUS AND OTHER NONHEMOLYTIC STREPTOCOCCI OF THE HUMAN THROAT. J. M. SHERMAN, C. F. NIVEN JR. and K. L. SMILEY, J. Bact. **45**:249 (March) 1943.

The authors studied in detail 331 cultures representing the predominating nonhemolytic streptococci of the human throat. They identified 184 strains as Streptococcus salivarius and the remaining 147 as members of the Streptococcus mitis group. The former appears to be a remarkably homogeneous and clearly defined species, especially marked by its ability to synthesize large amounts of polysaccharide from sucrose and to ferment both raffinose and inulin, its inability to produce considerable greening in blood agar, and many other correlating and apparently constant characteristics which should be of value in the clinical laboratory in the differentiation of these organisms from hemolytic streptococci. Furthermore, about 40 per cent of the strains of Streptococcus salivarius belong to serologic type I. The authors claim there is at least one other serologic type which includes a fairly large proportion of the strains of this species and an unknown number of other types. The so-called "streptococcus cardioarthritidis" because of its physiologic and serologic characteristics was identified as Streptococcus salivarius.

Streptococcus mitis represents a rather heterogeneous and perhaps complex group, giving diverse tests in many of the reactions studied. The group has, however, a considerable degree of homogeneity and can be readily differentiated not only from Streptococcus salivarius but from several other species of viridans streptococci.

STOESSER, Minneapolis.

COMPLICATIONS OF TONSILLECTOMY. R. N. MISRA, J. Indian M. A. **12**:108 (Jan.) 1943.

Misra, reviewing 2,078 cases of tonsillectomy, records the number of postoperative complications as follows: hemorrhage, 23; bronchitis, 1; exacerbation of pulmonary tuberculosis, 2; pulmonary abscess, 1; otitis media, 2; hyperpyrexia which yielded to sulfonamide drugs, 4; atrophy of the uvula, 1; deep cervical phlegmon, 1; surgical emphysema, 1; acute rheumatism, 1, and habitual dislocation of the jaw, 1. There were no cases in this series of cavernous sinus thrombosis, abscess of the brain or glottic spasm.

GONCE, Madison, Wis.

INTELLIGENCE TESTS FOR DEAF-MUTES. ROMULO E. FOSTER, Rev. de hig. y med. esc. **2**:100, 1943.

This work analyzes the results obtained from the application of some intelligence tests with such striking success that the intelligence quotient computed for each child coincides with the opinion of the capacity of the child previously formed by the teacher. Systematic application of these tests at the admission of each child to the National Institute (of Argentina) for the Deaf-Mute will serve as a means of future orientation and systematic grouping in the grades.

The tests were given to 137 deaf-mute children and to 12 children with defects in pronunciation.

[FROM THE AUTHOR'S SUMMARY.]

Diseases of Lungs, Pleura and Mediastinum

LIPID PNEUMONIA. ARTHUR M. STOKES, Am. Rev. Tuberc. **47**:348 (March) 1943.

A man 62 years old had symptoms and physical signs which indicated the presence of a malignant growth or abscess in the lung. During an exploratory thoracotomy the surgeons so strongly suspected the presence of a malignant growth that they removed the lower and middle lobes of the right lung. Microscopic examination revealed lipid pneumonia and an abscessed condition. Further inquiry into the patient's history elicited the facts that for several years he had used petrolatum freely in his nose on retiring, that for more than a year he had used a proprietary preparation containing oil and that he habitually slept on his right side.

EUGENE SMITH, Ogden, Utah.

TREATMENT OF CHRONIC EMPYEMA. P. R. ALLISON, Lancet **1**:232 (Feb. 20) 1943.

The aim of this paper on treatment of chronic empyema is not to present a new operation which is universally applicable or one which should necessarily displace other and well tried methods but to introduce a method of attack which the author found valuable on many occasions and which has the advantage of being less mutilating than many of the procedures now in use.

To gain access, resection of parts of one or two ribs near the base of the empyema cavity is necessary.

In the operation for chronic empyema described here, the cavity is obliterated by stripping the thickened parietal layer of the pleura from the wall of the chest and pressing it down on the visceral layer by means of a gauze pack; the new cavity produced in this way has fresh walls and heals quickly.

LANGMANN, New York.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

SPECIFIC PROPHYLAXIS AGAINST ENTERIC DISEASES. STUART MUDD, J. Bact. **45**:61 (Jan.) 1943.

The author makes a report on the causes of enteric diseases. He states that the extensive use of typhoid vaccine has reduced the incidence of this disease to such a low level that the diseases of the gastrointestinal tract caused by other organisms now predominate. Protection against the large residual group of paratyphoid fevers and Salmonella "food-poisoning" infections presents unsolved problems of considerable magnitude. Emphasis is placed on the fact that the reaction to whole bacterial vaccines sets definite limitations to the number of organisms and hence to the antigenic coverage which it is practicable to incorporate in whole bacterial vaccines. The best approach

will probably be in the direction of using dissolved surface antigens as immunizing agents. It must be remembered, however, that all gastrointestinal disturbances are not due to bacteria. During the cold season, when respiratory infections are prevalent, outbreaks of these disorders in households are commonly observed in which some members show mainly respiratory symptoms, others mainly gastrointestinal and still others both. The possibility that these infectious diarrheal conditions may be due to a virus or other as yet unidentified causal agent would seem to be well worth investigating.

STOESSER, Minneapolis.

AN ASSOCIATION OF GASTROINTESTINAL ALLERGY WITH THE CELIAC SYNDROME. CHARLES F. MCKHANN, SAMUEL SPECTOR and EMILY R. MESERVE, J. Pediat. **22**:362 (March) 1943.

Cutaneous tests of patients with the celiac syndrome made by the authors have in each patient revealed an allergy to certain foods. Elimination of these foods from the diet has resulted in clinical improvement, gain in weight and a return to normal stools. One patient was found to be allergic to banana and to orange juice, two foods ordinarily well tolerated by persons with celiac symptoms. Vitamin A absorption, which is extremely low in celiac disease, has been found to be extremely low in other allergic conditions also. There thus seems to be an association of gastrointestinal allergy with the celiac syndrome, although whether the allergy is the cause of celiac disease or celiac disease precedes the development of the allergy is admittedly not clear.

STETTENBENZ, Buffalo.

GASTRIC ACIDITY DURING THE FIRST YEAR OF LIFE. R. A. MILLER, Arch. Dis. Childhood **17**:198 (Dec.) 1942.

Gastric acidity during the first year of life shows a rapid rise in concentration with a probable increase in volume. At the end of this period the reaction of the stomach to a test meal of milk closely resembles that of an adult, for the maximum and average values are almost identical in the two age groups. Accompanying the development of the digestive powers of infants there is a diminution in the incidence of achlorhydria. The change applies to both true and false varieties of achylia, which is almost always transitory, not permanent; this fact corresponds to the modern conception of gastric secretory function in adults. The behavior of gastric secretion in infantile eczema and pyloric stenosis has also been studied. The results show that any disturbance of this function that may be observed in these diseases is certainly not primary but secondary.

KELLY, Milwaukee.

Nervous Diseases

PSEUDOJACKSONIAN EPILEPSY IN CHILDREN. JOHN E. SCARFF, Arch. Neurol. & Psychiat. **49**:223 (Feb.) 1943.

The author describes a specific clinical syndrome of unilateral convulsions in children, characterized by unilateral clonic jerkings beginning in both the arm and leg at the same time and without loss of consciousness. Hemiparesis sometimes accompanies the seizures.

Pneumoencephalograms revealed mild diffuse hypoplasia of the brain in 6 or 7 cases. Subcortical, calcified degenerated areas were found in 1 case and unusually dense pacchionian granulations in 4 cases.

Phenobarbital and diphenylhydantoin sodium have little effect on the seizures. Lysis of the abnormal pacchionian granulations produced improvement in 1 case, and removal of the calcified mass gave relief from the seizures and hemiparesis in another case.

BEVERLY, Chicago.

THE DIAGNOSIS AND PROGNOSIS OF BRAIN TUMORS. GILBERT HORRAX, Bull. New York Acad. Med. **19**: 125 (Feb.) 1943.

From the standpoint of diagnosis tumors of the brain fall into two main clinical categories: those which present well known symptoms and signs of tumor of the brain and those which show many different neurologic or other characteristics but lack the usual classic picture of this disorder. In the first group one deals with the time-honored triad headache, vomiting and choked disk. Here abscess of the brain and other inflammatory conditions producing the symptoms must be excluded. Likewise subdural hematoma, malignant hypertension and aneurysm of a cerebral blood vessel must be ruled out. The author cautions against spinal puncture in these cases. It is seldom necessary or helpful. While accidents are rare, he states, the danger is more than theoretic.

In the second group are patients who do not have choked disks and who in general present signs and symptoms which are as indefinite as they are inconstant. Thus they may experience convulsions, focal or generalized, slow visual failure, changes in personality and progressive hemiparesis—bizarre neurologic and psychologic syndromes which require meticulous evaluation and often lengthy observation.

Regarding the location and the pathologic characteristics of tumors of the brain they may again be divided into two groups. The first group includes the following types: those which as a rule can be recognized with a high degree of accuracy from the symptoms and the objective clinical signs; those which are benign, encapsulated and favorable for complete enucleation, such as meningiomas, acoustic neuromas, pituitary adenomas, some of the benign though uncommon cholesteatomas or slowly growing gliomas and those somewhat less favorable tumors, such as the congenital cysts of Rathke's pouch, pinealomas and some aneurysms.

In the second group are tumors which seldom or never give evidence of their location. This group includes many of the large infiltrating gliomas of all kinds which occupy the silent areas of the brain. By means of the ventriculogram some of these tumors may be detected in the cerebellum, above or below the tentorium or in the region of the third ventricle.

As to prognosis, a skilled neurosurgeon, with the assistance of a competent pathologist, should be able to express an opinion on the outlook for the patient after the operation. Obviously the most important factor is the nature of the tumor and the extent to which complete extirpation is possible.

JAHR, Omaha.

A NEW PYRAMIDAL SIGN OF GREAT FREQUENCY. LANE ALLEN and HERVEY CLECKLEY, J. Nerv. & Ment. Dis. **97**:146 (Feb.) 1943.

In an attempt to elicit from the toes a reflex comparable to the Hoffmann sign of the hand, Lane and Cleckley have discovered a new sign of disease of the pyramidal tract which they believe to occur frequently. With the leg relaxed and the foot in slight plantar flexion, the second toe is flicked sharply upward with the finger applied to the ball of the toe. A positive result is indicated by a quick and transient dorsiflexion

of the great toe and sometimes of the lesser toes. The maneuver is similar to that described by Rossolimo and sometimes elicits the Rossolimo reflex. The new sign, referred to as hallux extension, is extremely sensitive and may appear with slighter impairment of function of the pyramidal tract than is necessary to produce the Babinski or the Rossolimo sign. The authors suggest that the new sign may result from damage to area 6, and that it is an early and very sensitive, although not absolute, indication of pyramidal dysfunction.

CHODOFF, Langley Field, Va.
[ARCH. NEUROL. & PSYCHIAT.]

EFFECT OF INFRARED HEAT ON LOCALIZED POLIOMYELITIS AND NEURITIS. JOHN A. TOOMEY, J. Pediat. **22**:135 (Feb.) 1943.

By means of a 500 watt Tungsten bulb held 18 inches (45 cm.) away from the face for thirty minute intervals, Toomey tested the muscular response in 3 patients with paralysis of the seventh nerve due to poliomyelitis and 6 patients with peripheral neuritis of the seventh nerve. Prior to treatment, none of the patients could move the facial muscles, but after infra-red therapy those with poliomyelitis were able to move the muscles for short periods; none of the patients having a peripheral neuritis were able to do this. Thus Toomey contends that there must be intact nerve fibers connecting undamaged neurons in order for these patients to have movement of muscles. It is thus logical in patients with poliomyelitis to maintain muscle tone, best accomplished by the application of heat (infra-red radiation or Kenny's hot foments), until maximum nerve function returns. Some idea of prognosis may be obtained through the use of infra-red heat since for those patients in whom no muscular response is obtained after three to four weeks the outlook is indeed bad.

STETTENBENZ, Buffalo.

Psychology and Psychiatry

THE PSYCHIATRIST AND THE BEHAVIOR PROBLEM. ALBERT B. SIEWERS, New York State J. Med. **43**: 328 (Feb. 15) 1943.

The psychiatrist, the pediatrician and the psychiatric social worker need to cooperate if the causes back of any behavior problem are to be discovered. Careful studies of the whole family problem are required.

AIKMAN, Rochester, N. Y.

Diseases of the Genitourinary Tract

CRYPTORCHIDISM. JOSEPH H. LAPIN, WILLIAM KLEIN and ALEX GOLDMAN, J. Pediat. **22**:175 (Feb.) 1943.

Of 200 patients with cryptorchidism treated in an endocrinology clinic by Lapin, Klein and Goldman, only 39 had follow-up adequate to justify presentation. Complete success was attained in only 6 cases. In 4 of the 39 patients hypogonadism and eunuchoid proportions developed, which raises the question as to whether endocrine therapy in some cases may produce hypogonadism. The procedure in treating these patients should be one which will avoid the dangers of testicular atrophy. The authors have adopted the following recommendations: 1. Treatment of cryptorchidism is advisable. 2. The optimal age is 14. 3. A preliminary test of endocrine therapy is justified if the testes are not clearly ectopic. 4. Chorionic gonadotropin (human pregnancy urine preparation) is the only medicament free of theoretic objections. 5. The maximum dose should not exceed 6,000 international units. 6. The dosage should be continued over a six week interval without any rest periods. 7. If no descent follows this regimen, an operation should follow immediately and endocrine treatment should be given after implantation. 8. Patients with ectopic testes should have preoperative and postoperative endocrine therapy.

STETTENBENZ, Buffalo.

THE INVESTIGATION OF RENAL FUNCTION WITH A NEW NOMOGRAPHIC METHOD FOR THE DETERMINATION OF UREA CLEARANCE. M. C. DAVIS, M. J. Australia **1**:267 (March 27) 1943.

Sixty-seven tests of renal function were performed in a series of 54 cases, and a comparison was made of urea clearance, urea concentration, blood urea level and clinical condition of the patient. The necessity for giving urea by mouth when testing the clearance was established. Oral administration of urea as a preliminary to the test was based on the principle that for adequate and complete assessment of renal activity the kidneys must be subjected to a test involving stress akin to that caused by operation or the like. Frequently, when the results of simple estimations of blood urea and tests of urea concentration were normal the urea clearance test after 15 Gm. of urea had been given by mouth revealed considerable renal defect. Damage to the kidneys must be fairly advanced before the level of urea in the blood becomes elevated, and the results of urea concentration tests will be misleading if the volumes are ignored. The urea clearance test, by taking into consideration the interdependence of factors, allows a more exact assessment of functional renal reserve and therefore a more accurate prognosis. A simple nomographic chart is presented, which, from a knowledge of the blood urea level, the urea concentration and the volume of urine excreted per minute, permits determination (without mathematical formulas) of the true value for urea clearance.

GONCE, Madison, Wis.

Diseases of the Ductless Glands; Endocrinology

PURPURA FULMINANS (WATERHOUSE-FRIDERICHSEN SYNDROME): REPORT OF A CASE WITH RECOVERY. W. L. RUCKS and J. J. HOBSON, J. Pediat. **22**:226 (Feb.) 1943.

The case of a 3 year old boy who recovered from purpura fulminans is reported in detail. This is the third case in the literature in which the patient survived. Significant in the therapy, and believed to be responsible for the recovery, was the use of cortical extract to replace the hormone lost through adrenal hemorrhage and the use of one of the sulfonamide drugs, sulfathiazole. No etiologic bacteria were recovered in this case; Staphylococcus aureus, first obtained in blood culture, was believed to be a contaminant. At the time of the report, eleven months after recovery, the patient was well and there had been no unfavorable sequelae.

STETTENBENZ, Buffalo.

Diseases of the Eye

CHORIORETINITIS ASSOCIATED WITH POSITIVE SEROLOGIC TESTS FOR TOXOPLASMA IN OLDER CHILDREN AND ADULTS. D. VAIL, J. C. STRONG and W. V. STEPHENSON, Am. J. Ophth. **26**:133 (Feb.) 1943.

The authors give the following summary:

"Six cases of chorioretinitis of previously unknown etiology are reported in which the presence of positive neutralization antibodies for Toxoplasma was proved.

The condition may be either congenital or acquired. The only symptom may be that of poor or decreasing vision. The fundus usually reveals a chorioretinitic lesion, unilateral or bilateral, having a predilection for the macular area. It has a grayish white center and is irregular, bordered with dark pigment and surrounded on one or more sides by faint choroidal hemorrhage. The spread of the lesion is usually in the direction of the hemorrhage. The lesion may be elevated. Iridocyclitis, vitreous opacities, retinitis proliferans and detachment of the retina may result. Central vision is always adversely affected."

REESE, Philadelphia. [ARCH. OPHTH.]

VISION TESTING IN ILLINOIS. AUDREY M. HAYDEN, Illinois M. J. **83**:175 (March) 1943.

Since 1936, tests of visual acuity have been given to 1,466,510 school children in Illinois, under the joint aegis of the Works Progress Administration and the Illinois Society for the Prevention of Blindness. Of this number, 77,497 children were found to have defective vision, and in this period 52,807 children had their vision corrected. From March 1, 1941 to March 1, 1942 corrections of vision were made for 15,007 children. Of this number 5,427 went to ophthalmologists, 2,949 to clinics, and 6,631 to optometrists.

BARBOUR, Peoria, Ill.

THE PROBLEM OF THE HYPERMETROPIC MINER. A. C. REID, Brit. J. Ophth. **27**:110 (March) 1943.

Reid points out that the myopic miner who consistently wears his correction above ground can dispense with glasses below ground. This is not true of the miner with high hypermetropia, who has to accommodate to see his work, since a miner's work is done mostly within arm's length. Fourteen cases of hyperopia of high degrees are recorded to show the points the author wishes to raise. Seven of the patients who had an error of between 2 and 4 in the lowest axis averaged 37 years of age, the extremes being 28 and 44. With a + 4 D. error few men can go beyond the age of 30 at the coal face. With an error of + 6 D. or more, probably no man should go below, and few do. It would therefore seem reasonable to advise lads with both eyes good not to go down if the error is + 3 D. or more and squinters or men with amblyopia not to go down at all. Much can be done in advising the parents when a boy is about to leave school.

ZENTMAYER, Philadelphia. [ARCH. OPHTH.]

Skin Diseases; Allergy

SYMMETRIC NEVI OF FACE, TUBEROUS SCLEROSIS, EPILEPSY AND FIBROMATOUS GROWTH ON SCALP, WITH ABNORMAL ELECTROENCEPHALOGRAMS OF MEMBERS OF THE FAMILY. CHARLES K. GOOD and JOHN GARB, Arch. Dermat. & Syph. **47**:197 (Feb.) 1943.

Good and Garb report the case of an American-born woman aged 29 with an Italian mother and a French father who were not consanguineous. A hairless, smooth "red birth mark" was noted on the scalp at birth. At the age of 9 years this "mark" began to grow, increasing in diameter and thickness.

The patient was the second oldest of 6 girls. One sister, aged 21, was "nervous and irritable." Another, aged 15, had a congenital deformity of the cervical portion of the spine and unilateral deafness, which followed otitis. Another sister, aged 12, had bilateral nephroptosis, with angulation of the left ureter. The other members of the family presented nothing of interest. The serologic reactions of all the siblings were negative.

In the case cited, three small red "blotches" appeared first in the left malar region at 8 months of age. Similar lesions developed on the root of the nose and the right cheek and spread downward bilaterally to the mandible and chin. The maximum development of these lesions, numerically and in surface area, was attained at the age of 3 years. At 10 years of age the lesions began to grow, appearing as wartlike projections. After 16 years of age the mandibular lesions regressed, while the others became larger.

At the age of 4 years, the patient began to show signs of abnormal nervous irritability, such as supraorbital headache, frequent crying spells and attacks of stubbornness. These spells of stubbornness were followed by an abrupt change of mood, during which the patient became docile. At this time she began to have convulsive seizures. At 6½ years of age the typical epileptic spells became distressing, one attack following another in rapid succession. At this time the condition reached a turning point, and general improvement followed. After this she never lost consciousness, but until within three or four months of the time of this report she had "nervous spells." The attacks of stubbornness persisted.

The lesion of the scalp appeared as a large, sharply demarcated, almost hairless, hard growth. The facial lesions were distributed in butterfly fashion and were pinhead sized to split pea sized. Intermingled with the lesions of the face were numerous pinhead–sized to hemp seed–sized fibromas. On the forehead were numerous yellowish brown spots. Many filiform, verrucous projections occurred along the right axilla.

Neurologically the patient showed hyperactive tendon reflexes and absence of the right plantar reflex. She had frequent episodes of absences associated with grimacing movements. She was easily irritated. A retrograde pyelogram revealed abnormalities of the right kidney and the left ureter. The electroencephalogram revealed diffuse abnormal cortical activity. A tracing made five months earlier revealed a borderline normal state. The patient had borderline intelligence. The histologic diagnosis of one of the lesions of the face was fibroma, and the lesion of the scalp was also interpreted as being of fibromatous structure.

The electroencephalogram of the father, aged 42, was interpreted as representative of a "latent" convulsive disorder; that of a sister, aged 22, indicated diffuse abnormal cortical activity. A sister, aged 18, showed diffuse cortical involvement, but to a lesser degree; a sister, aged 16, showed a mild degree of diffuse involvement.

The authors suggest that the electroencephalogram may prove valuable in discovering abortive types of tuberous sclerosis in members of a family and close or distant relatives of a person with epiloia. They point out that epiloia is frequently characterized by long remissions, during which the mental deterioration progresses after the convulsions have subsided.

SANDERS, Philadelphia.
[ARCH. NEUROL. & PSYCHIAT.]

FATALITIES AND CONSTITUTIONAL REACTIONS FOLLOWING THE USE OF PONTOCAINE [TETRACAINE HYDROCHLORIDE]. J. WARRICK THOMAS and MERYL M. FENTON, J. Allergy **14**:145 (Jan.) 1943.

The article reviews the question of sensitivity to tetracaine hydrochloride as characterized by constitutional reactions occurring when this drug was used as

an anesthetic during bronchoscopy, gastroscopy and dental extraction and in ophthalmologic practice. There have been at least three fatalities. It is important to bear in mind the possibility of such sensitivity when the use of tetracaine hydrochloride is contemplated for an allergic person. A patch test may aid in determining sensitivity.

HOYER, Cincinnati.

KOCHIA SCOPARIA AS A FACTOR IN INHALANT ALLERGY. OREN C. DURHAM, J. Allergy **14**:160 (Jan.) 1943.

Kochia scoparia (Mexican fireweed, fireball, firebush or summer cypress) has been introduced in some localities as a cultivated shrub. However, in some areas, it has become a weed whose pollen needs to be thought of as a cause of hay fever. It has spread rapidly in eastern Colorado, western Kansas, the Dakotas, western Iowa and Nebraska and in some of the urban centers as far east as Detroit and as far south as St. Louis. The plant is a successful rival of Russian thistle and is already replacing ragweed locally.

HOYER, Cincinnati.

THE USE OF VITAMIN B COMPLEX IN THE TREATMENT OF INFANTILE ECZEMA. AARON HARRIS and LESLIE N. GAY, J. Allergy **14**:182 (Jan.) 1943.

Twenty patients with eczema, children ranging in age from 6 months to 12 years, were given a preparation of vitamin B complex. The authors concluded, "While we were unable to obtain the uniformly excellent results obtained by other workers, we feel that vitamin B complex in some cases is a valuable adjunct in the treatment of eczema."

HOYER, Cincinnati.

Surgery and Orthopedics

THE PRINCIPLES OF TREATMENT OF CLOSED HEAD INJURY. D. DENNY-BROWN, Bull. New York Acad. Med. **19**:4 (Jan.) 1943.

Closed head injury is defined as a severe injury to the head not essentially lacerating the scalp or fracturing the bones of the skull. The author presents an excellent review of the pathologic features, the symptoms and the treatment of the condition in its various clinical stages.

JAHR, Omaha.

Miscellaneous

THE EXERCISE TOLERANCE TEST AS A MEASURE OF CHRONIC FATIGUE IN CHILDREN. RALPH E. NETZLEY, J. Pediat. **22**:194 (Feb.) 1943.

A modification of the Schneider test has been used to determine evidence of chronic fatigue in children. Scoring can be readily and accurately done. The Schneider test is based primarily on the fact that with improvement in physical fitness the heart beats less frequently and more efficiently; a slow pulse in recumbency and standing, with small difference between the two, is a sign of good health. The author found that children with evidence of chronic fatigue, such as nervous instability, poor concentration, poor sleeping habits and appetite, tenseness and inability to relax, showed low tolerance to exercise. Patients with endocrine, allergic or cardiac disease also had low scores. The test may be used to determine the amount of rest necessary; periodic testing gives an index of progress until the desired scores are obtained.

STETTENBENZ, Buffalo.

SULPHAMETHAZINE (2-4'-AMINOBENZENESULPHONYLAMINO-4:6-DIMETHYLPYRIMIDINE): A NEW HETEROCYCLIC DERIVATIVE OF SULPHANILAMIDE. F. L. ROSE, A. R. MARTIN and H. G. L. BEVAN, J. Pharmacol. & Exper. Therap. **77**:127 (Feb.) 1943.

The results of experiments on a small series of both normal and sick persons indicate that sulfamethazine is freely and rapidly absorbed by man and does not give rise to toxic symptoms or renal complications even when given in large doses, and hence may have advantages over the other sulfonamide compounds in use.

PILCHER, Cleveland.

THE EFFECT OF SODIUM CITRATE ADMINISTRATION ON EXCRETION OF LEAD IN URINE AND FECES. T. V. LETONOFF and SEYMOUR S. KETY, J. Pharmacol. & Exper. Therap. **77**:151 (Feb.) 1943.

Previous papers have reported a significant decrease in the concentration of lead in the blood after administration of sodium citrate in cases of lead poisoning. In this study it was found that there was a considerable increase in fecal and urinary excretion of lead, usually greater in the feces than in the urine; also there was a significant drop in the amount of lead in the blood. The study was made on 9 subjects who had been exposed to industrial lead hazards for several months to several years and of whom all but 1 showed signs of lead poisoning. It is well to bear in mind that lead poisoning occurs occasionally in infants and children and is usually severe.

PILCHER, Cleveland.

STUDIES ON SULFONAMIDE-RESISTANT ORGANISMS: III. ON THE ORIGIN OF SULFONAMIDE-RESISTANT PNEUMOCOCCI. L. H. SCHMIDT and CLARA L. SESLER, J. Pharmacol. & Exper. Therap. **77**:165 (Feb.) 1943.

Studies were made on a strain of Pneumococcus which had been passed either daily or on alternate days through mice for four years. The strain had never been exposed to a sulfonamide compound. The gist of the work is expressed in one sentence: "These findings support the conclusion that highly resistant pneumococci are formed as a result of some action of the sulfonamide on the sensitive organism."

PILCHER, Cleveland.

Society Transactions

CHICAGO PEDIATRIC SOCIETY

PHILIP ROSENBLUM, M.D., *in the Chair, Symposium on the Management of Poliomyelitis*

Oct. 19, 1943

Clinical Aspects. DR. A. M. WOLF.

What one does for a patient with acute poliomyelitis depends not only on the general status of the patient but on the daily variations in that status. What may be good general therapy at one time may require modification, even within a few hours, particularly in those instances in which there is bulbar involvement. During the apparently preparalytic phase and in cases without paralysis the general treatment is that given for any acute illness. Vitamin therapy is advocated by some, and it will do no harm if the dosage is kept within reason. Adequate intestinal elimination is considered of great importance by others. Acute poliomyelitis is a self-limited disease, however, and too much emphasis need not be placed on daily bowel movements. The diet should be as hearty and as complete as the patient will take.

Should there be bulbar involvement, however, all rules on diet and fluids definitely change; the mechanism of swallowing is attacked, and taking of food becomes a hazard. In general, in preparalytic and nonparalytic phases of the disease the patient should be left alone aside from the usual nursing; sometimes, in enthusiasm, more is done than Osler's law would permit. This is true also when there is involvement of the upper or lower extremities without additional complications.

If the lower extremities are involved, there may be paresis of the bladder, which need not be a cause for alarm, since it is temporary; the urinary difficulty usually clears up in a few days. I make every effort to obtain spontaneous voiding if possible, although with the use of sulfonamide drugs I do not have the old fear of catheterization. Neostigmine may be tried; I have seen no benefit from it. Warm enemas and hot stupes are more helpful.

Patients with bulbar involvement present an acute problem. In some years there are few; in others they may constitute a large proportion of the total number. The status of the patient may shift in a spectacular manner within a few hours. Some patients with the bulbar types of poliomyelitis when seen at home have seemed to have a mild attack; when they reached the hospital a few hours later one almost wondered if they were the same children. Probably transportation is a factor. These patients should be handled with the utmost care and should not be moved from hospital to hospital. All arrangements should be made prior to transportation.

Patients with bulbar poliomyelitis present a tremendous range of possible conditions. Abortive bulbar poliomyelitis is often seen; the patients come under observation after the acute phase is past and the temperature has become normal. Other patients have difficulty in swallowing but are still able to dispose of saliva and nasal secretions. In more serious attacks the patient may have a pool of mucus in the throat, indicative of his inability to get rid of this material. If he can swallow, feeding may be attempted cautiously, with bland food in small amounts, as tolerance permits. If the patient cannot dispose of his secretions, the administration of anything by mouth is contraindicated. One need not worry about a child not getting nutrition during the few days which will either see him through the terrible ordeal or see him die. Every effort should be made to get water and dextrose into the child and to maintain fluid balance, so that secretions in the throat will be thin and removable, not thick and tarry. The patient should be placed on his abdomen, with his head turned to one side. Care should be taken that the foot of the bed is elevated, so that the hips are higher than the shoulders.

Sometimes secretions will drain from the mouth spontaneously; sometimes suction must be applied, preferably with an old soft rubber catheter. Should cyanosis develop, even in a slight degree, the administration of oxygen is indicated and should be continued until one is sure the patient is out of danger. Not infrequently the patient breathes with an irregularity in tempo, depth or both, and the question of need for the respirator may arise. Its use in the treatment of bulbar poliomyelitis is to be condemned.

The test for need of the respirator is easily made. When its use is indicated it brings spectacular relief; however, when a patient with pure bulbar poliomyelitis is placed in the respirator it can be seen that more harm than good results. The patient breathes with the machine at times and against it at others. The use of the respirator under these conditions may be extremely harmful.

The peripheral type of respiratory palsy may develop in patients with bulbospinal poliomyelitis. It is more frequently found, however, in persons with pure spinal poliomyelitis with involvement of the arms, usually centripetal. For these patients the use of the respirator is definitely indicated and is life-saving. The earliest symptom of peripheral respiratory palsy may be restlessness. The patient's statement that he is not getting enough air is a warning that should not be ignored. The pulse may be accelerated; breathing may be more rapid and shallow, and, finally, cyanosis may occur. Cyanosis in peripheral respiratory failure is an indication that the respirator should have been used earlier. Once in the respirator, the patient should be kept there through the acute febrile stage of the illness and then permitted a few more days of rest within the machine, until he tolerates, without protest or excitement, the simple procedure of opening the porthole in connection with nursing care. Then one is ready for the big psychic problem of getting the patient to try to do his own breathing. The machine should be opened for a minute or two daily and the patient encouraged to breathe. After a few efforts he will do so, and thereafter the time the machine is kept open may be gradually increased.

General care in the acute phase obviously blends into convalescent care. Twenty-one days from the time of onset of the illness isolation is discontinued.

Special Aspects of Poliomyelitis in 1943. DR. S. O. LEVINSON.

In some aspects the 1943 outbreak of poliomyelitis differs from those usually occurring in this area. In the first place the curve of incidence was surprising.

Ordinarily, if there is going to be a heavy incidence a few cases occur in May or June and increased numbers in July and August. In this outbreak, however, May was a peaceful month and pediatricians were more concerned with virus pneumonia; only a few cases were reported throughout the state. The incidence was light in June and not heavy in July, but in August the curve rose steeply, and in the first and second weeks of September there was an average of 15 to 20 cases a day. The tapering off was not so rapid as the rise; cases of acute poliomyelitis are still occurring.

As a rule, an increased incidence of the disease in Chicago means an increase throughout the state; this year practically all cases were in Cook County or adjacent counties. The incidence of bulbar poliomyelitis was high. In one suburb in Cook County, in 10 of 13 patients the disease was of the bulbar type. The high incidence of bulbar poliomyelitis reflects the fact that one was dealing with a more severe form of the disease than has been seen in sporadic years or former epidemic years, inasmuch as the greater percentage of deaths occur in persons with that form of the disease. In addition, when bulbar poliomyelitis was seen formerly, usually it was the pure bulbar type—paralysis of areas innervated by the palatine and facial nerves, but rarely of the extremities. This year it was not unusual to find paralysis of the extremities associated with bulbar paralysis. There were also instances in which there was no paralysis of the extremities yet in which the condition was not frankly bulbar but rather encephalitic, the principal sign being pronounced disorder of the sensorium. Formerly this sign was considered a point of differentiation between poliomyelitis and encephalitis. The question can still be raised whether these were cases of encephalitis due to another virus. It was not possible to carry out a true study of the virus, but there is clinical confirmatory evidence of poliomyelitis in that some of the patients with this type of encephalitis had flaccid paralysis of the extremities as well as great disorder of the sensorium. In some instances the reactions simulated those typical of encephalitis due to measles, such as screwing of the face and high-pitched screaming. Up to the present time at least this condition has not been followed by the sequelae of encephalitis due to measles.

The usual course of therapy with convalescent serum, outlined by the state department of public health, was followed. Obviously the amount of serum available was barely sufficient. Convalescent serum was employed for the persons with preparalytic or bulbar poliomyelitis; pooled adult serum in larger amounts was used for those with paralytic poliomyelitis. There are not yet sufficient data concerning the cases which occurred this year to permit an evaluation of the results of serum therapy. Many patients will be followed in the clinic, but it will be some time before a final determination can be made.

The opinion as to the value of serum is still in a state of flux. S. D. Kramer, who worked with the Harvard poliomyelitis commission, was in 1932 a pronounced antagonist of the use of serum. He has since been working with the Lansing strain of poliomyelitis and has studied the value of convalescent serum in the mouse. He has found definite evidence not only that convalescent serum neutralizes the virus and protects the mouse but that inoculation with serum ninety-six hours after inoculation with the virus protects the animal in a significant number of instances. He has also made observations on the relation between the dose of serum and the weight of the animal and has furnished experimental proof for a long-established clinical practice, the regulation of the dose of serum in relation to the body weight of the patient as well as the severity of the infection.

Pathologic Changes in Poliomyelitis. Dr. Otto Saphir.

During the recent epidemic 17 autopsies were performed on patients who died of poliomyelitis. In practically every instance, the brain and the spinal cord were involved.

In the brain the pathologic changes were most evident in the regions surrounding the ventricles. These changes were summarized as: (1) degenerative changes in ganglion cells; (2) inflammatory changes, with predominance of round cells and polymorphonuclear leukocytes, and (3) foci of necrosis in the walls of small blood vessels, with small or large hemorrhages. In the spinal cord the lesions were not all confined to the anterior horn; the posterior horn was also involved and occasionally the white substance.

In each instance severe hyperemia of the visceral organs was encountered, particularly evident in the liver and kidneys. The abdominal lymph nodes, particularly those in the ileocecal regions, were enlarged, and histologic examination disclosed simple lymphoid hyperplasia with special involvement of the germinal centers. Similar changes were encountered in the spleen and in the solitary follicles in Peyer's patches. It is noteworthy that the 2 adults in this series did not have the severe lymphoid hyperplasia found in the children.

Lesions in the respiratory tract were frequent. The basal membranes of both the trachea and the bronchi were thickened, and there were infiltrations of polymorphonuclear leukocytes and a few lymphocytes in the submucosa. In the lungs severe edema was not always present, though it had been expected clinically. The usual features were early interstitial pneumonia and atelectasis in dispersed foci.

A careful study of the heart disclosed acute myocarditis in the majority of instances. Inflammatory cells were found both in the interstitial tissue and replacing severely degenerated and necrotic fibers of cardiac muscle. The degree of myocarditis varied; in some instances it was of a serous type, with only a few inflammatory cells, while in others it was extremely cellular.

The neuromuscular apparatus (myoneural junction) is not discussed because study of these structures has not been completed.

Atypical Poliomyelitis. Dr. J. P. Reich.

The question as to whether the so-called cerebral and cerebellar forms are true manifestations of poliomyelitis is still under discussion. The results of certain experimental studies would indicate a lack of identity of the virus which causes true poliomyelitis and that which invades the higher levels of the central nervous system. On the other hand, there are instances in which the onset and the general signs are those characteristic of poliomyelitis but the neurologic signs point to a different location of the infection. One seems justified in classifying such conditions as "atypical forms" of poliomyelitis, the more so as many anatomic changes are found in the cerebrum and cerebellum in persons with this form of the disease. Speaker mentioned that during the epidemic of 1932 in Silesia changes in the optic nerves were found in 5 of 22 patients.

With respect to treatment, galvanotherapy of the paralyzed muscles is recommended. It is the only method which produces contractions of the muscles and

thus puts them in more favorable condition for reinnervation. Recent experimental results speak in favor of this method.

Differential Diagnosis. DR. J. K. CALVIN.

In the course of this epidemic, when more than 200 patients were admitted to Michael Reese Hospital, it was natural that a number of persons were sent in as poliomyelitic who subsequently proved to be otherwise.

The differential diagnosis of poliomyelitis must be considered in relation to the clinical picture at different stages of the disease. In general the course may be divided into (1) the prodromal febrile stage, without meningeal signs, when a specific diagnosis cannot be made; (2) the preparalytic stage, with meningeal irritation and spasm, and (3) the paralytic stage, in which there is not much problem in differential diagnosis, except of the bulbar type of the disease. During these past months every patient with fever and meningeal irritation was suspected of having poliomyelitis. The diagnosis depended on this suspicion and evidence obtained by lumbar puncture. Such conditions as postdiphtheritic paralysis and toxic neuritis, although not encountered here, are usually obvious. Pseudoparalysis due to pain from scurvy, arthritis and osteomyelitis may be confusing.

Four cases which are of particular interest from the standpoint of differential diagnosis are briefly summarized.

CASE 1.—R. R., a boy aged 5½ years, stuck a stick into his left cheek ten days before admission to the hospital. Several days later he had difficulty in swallowing, some difficulty in opening the mouth and complete paralysis of the regions innervated by the left facial nerve. On admission these conditions were still present; the neck was moderately rigid; the sensorium was clear; the temperature was normal and there were no other signs. The differential diagnosis lay between tetanus and bulbar poliomyelitis, because of the nuchal rigidity, difficulty in swallowing and facial paralysis (occurring rarely in tetanus). The presence of an infected wound, the trismus, the normal condition of the spinal fluid and the absence of fever pointed toward tetanus. Within forty-eight hours the appearance of unilateral risus sardonicus, boardlike rigidity of the abdomen, asphyxial glottic spasms and generalized tonic convulsions confirmed the diagnosis. Urinary retention may occur in both conditions.

Cephalic tetanus due to wounds along the distribution of the cranial nerves may at first show only spasms confined to the muscles of the jaw, pharynx and esophagus. Rarely benign peripheral paralysis of the seventh nerve on the side of the lesion occurs, as in this patient.

Tetanus was the final diagnosis.

CASE 2.—Twin girls aged 8 months were sent in as possibly having poliomyelitis because for the previous week they had been irritable, had stopped crawling and sitting up, had not moved their legs and had screamed when the legs were touched or moved. They had received Kenny treatment for two days at home. On admission the children lay with their legs in semiflexion and external rotation, would not move them or sit up and cried when handled. No fever was present. They showed the hemorrhagic condition of the gums around the erupting incisors, the angulated beading of the ribs and the roentgen evidence typical of scurvy. They had had no orange juice, because it disagreed with them, according to the mother.

Scurvy was the final diagnosis.

CASE 3.—A. A., a boy aged 4 years, had been irritable, with some fever, off and on for two weeks. The day before admission to the hospital he became semicomatose and remained so for two days; then a stuporous delirium developed, lasting several days. During this time his temperature ranged between 100 and 101 F. Some rigidity of the neck was present. The spinal fluid contained 150 cells per cubic millimeter, 90 per cent of which were lymphocytes, and reacted positively to the Pandy test. The child had been definitely exposed to open tuberculosis within the past four months. The differential diagnosis involved polioencephalitis, other forms of encephalitis and tuberculous meningitis. The normal content of sugar in the spinal fluid eliminated the possibility of tuberculous meningitis. Poliomyelitis serum was given intravenously, and within four days after admission the child became mentally clear and cooperative. Definite muscular weakness was then detected in the right anterior tibial muscle, the left deltoid muscle and the muscles of the left side of the face. Spasm was present in the hamstring muscles and in those of the back. Within three weeks these conditions had disappeared.

Poliomyelitis was the final diagnosis.

CASE 4.—J. C., a boy aged 8 years, had fever, vomiting and headache for three days before admission to the hospital. On entering the hospital he had a temperature of 103 F. and evidence of extreme meningeal irritation. The neck and back were especially rigid. Otherwise, physical examination showed him to be essentially normal. A slight cough developed. The spinal fluid was normal. However, the leukocyte count was 34,000, with 90 per cent of the cells polymorphonuclear leukocytes, an unheard of count in uncomplicated poliomyelitis. Roentgenograms revealed definite pneumonia. The fever responded to sulfonamide drugs within twenty-four hours. The rigidity of the back and neck and the spasm of the muscles of the back and neck and of the hamstring group persisted for more than a week. No muscular weakness developed.

Pneumonia was the final diagnosis.

News and Comment

GENERAL NEWS

American Board of Pediatrics, Inc.—The American Board of Pediatrics will hold a written examination on Sept. 22, 1944, locally, under a monitor, for all applicants taking oral examinations in the fall.

Oral examinations will be held in St. Louis on November 8 and 9, preceding the annual meetings of the American Academy of Pediatrics and the Southern Medical Association, and in New York on November 9 and 10.

Physicians Certified by the American Board of Pediatrics.—The following physicians were certified as specialists by the American Board of Pediatrics after the examinations in New York on March 25 and 26, 1944:

Louis Thobro Campbell, Saranac Lake, N. Y. (in the Army); Cornelia Morse Carithers, Jacksonville, Fla.; William Andrew Daniel Jr., Montgomery, Ala.; Thomas Albert Foster, Portland, Me.; Mariana Gardner, Denver; A. Louis Girardin Jr., Fort Myers, Fla. (in the Army); Joseph Glassman, Brooklyn; Henry Mitchell Glaubman, Hartford, Conn.; Solomon Goodman, Brooklyn; John L. Green, Philadelphia; Martin Green, Philadelphia (in the Navy); Joseph James Greenlaw, Washington, D. C.; Robert Dean Hart, Peoria, Ill. (in the Army); Akiba Joseph Himmelhoch, Detroit (in the Army); Ng. William Hing, Puerto Rico (in the Army); Martin Joseph Hurst, Kansas City, Mo. (in the Army); Gertrude Martina Hyde, Port Chester, N. Y.; Nina R. Lief, Far Rockaway, N. Y.; Alla Dunewitz-Litvak, Brooklyn; Lula O. Lubchenco, Denver; Robert Alister McGuigan, Evanston, Ill. (in the Navy); Robert Dickie Nix, Mt. Lebanon, Pa. (in the Army); Israel J. Rosefsky, Binghamton, N. Y.; Russell E. Sangston, Uniontown, Pa. (in the Navy); Sydney Milton Saul, Pittsburgh; Lillian Shulsky, Brooklyn; Theresa Ora Snaith, Weston, W. Va.; Harold E. Stadler, Indianapolis (in the Army); Leon Sternfeld, Buffalo; Alfred J. Vignec, New York; Richard Wagner, Boston; David H. Weintraub, Buffalo; Arnold H. Williams, Laurel, Del.

Publication in Honor of Profesor Hurtado y Galtés.—The pamphlet "Veinticinco años después" (Habana, 1943), published in appreciation of twenty-five years of practice by Prof. Félix Hurtado y Galtés, was received recently. The publication constitutes a worthy compliment to the eminent Cuban pediatrician.

PERSONAL NEWS

New Appointments for Dr. John D. Lyttle.—Dr. John D. Lyttle, formerly of the department of pediatrics, College of Physicians and Surgeons of Columbia University in New York, has recently accepted the position of professor of pediatrics in the School of Medicine of the University of Southern California and the position of director of pediatrics at the Children's Hospital in Los Angeles.

Book Reviews

Principles of Orthodontics. By J. A. Salzmann, D.D.S. Price, $10.00. Pp. 674, with 450 illustrations and 35 tables. Philadelphia: J. B. Lippincott Company, 1943.

The most significant development in the special field of dentistry which is concerned with prevention and correction of malocclusion of the teeth is the recognition that this orthopedic service is associated with both general and regional physiologic and pathologic processes. Notwithstanding the importance of mechanical devices and technics which have deserved and received considerable attention in the past, the specialists in this field have come to realize that the local condition bears an intimate relation to the physiologic phenomena of heredity, growth, development and function. Likewise they understand that causation, diagnosis, preventive therapy and corrective measures in cases of malocclusion of the teeth and facial deformities rest on a knowledge not only of the normal structures but of the manner in which disease affects the form, the function and the reactivity of the tissues with which orthodontists have to deal and the entire body economy with which these tissues are integrated.

Dr. Salzmann is the first author of an orthodontic text to give a systematic and a detailed consideration of this foundation essential to the special field. In chapters 3 to 11 he has furnished a well chosen review of much of the best material pertinent to the subject. Growth and developmental processes of the entire body as well as of the face and the oral structures are included. One chapter is devoted to the relation of the endocrine glands to dentofacial deformities, while in another chapter the contribution of nutrition is given special attention. Modern methods of examination and diagnosis are furnished, and preventive measures are discussed. The principal devices of mechanical therapy are briefly given in 74 of the 674 pages.

For the physician and the medical student interested in correlating an understanding of malocclusion with his knowledge of the child as a whole and for those who wish an acquaintance with the field of orthodontics, this volume is perhaps the best single source of information.

Puericultura (Higiene alimentare e social da criança). By Prof. Martagão Gesteira. Price, not given. Pp. 495, with 109 illustrations. Rio de Janeiro: Pan Americana S. A., 1943.

The first part of this book deals with the problems of infant feeding and the disturbances of digestion. Considerable space is given to breast feeding and methods for stimulating the breasts. This is much more detailed and minute than is ever given in similar textbooks in English. The last part of the book discusses the methods by which a state or country can best organize a program for infant care. The illustrations of some of the clinics and hospitals, such as the Abrigo Maternal da Baia and the Pupilheira Juracy Magnalhaes, show that our southern neighbors have nothing to learn from us in beautiful and spacious buildings. Any one interested in child welfare will find this book extremely interesting; and its perusal leaves the reader just a little envious of the breadth of understanding of the Brazilian people.

Directory of Pediatric Societies *

INTERNATIONAL

International Association of Preventive Pediatrics

President: Prof. S. Monrad, Dronning Louises Børnehospital, Copenhagen, Denmark.
Secretary: Dr. Daniel Oltramare, 15 Rue Lévrier, Geneva, Switzerland.

International Congress of Pediatrics

President: Dr. Henry F. Helmholz, Mayo Clinic, Rochester, Minn.
Secretary-Treasurer: Dr. Charles F. McKhann, University Hospital, Ann Arbor, Mich.
Canadian Committee:
Chairman: Dr. Alan Brown, Hospital for Sick Children, 67 College St., Toronto.
Secretary: Dr. H. P. Wright, 1509 Sherbrooke St. W., Montreal.
Place: Boston. Time: Postponed indefinitely.

International Congress for the Protection of Infancy

Secretary: Prof. G. B. Allaria, Corso Bramante 29, Torino 120, Italy.

FOREIGN

Argentine Pediatric Society of Buenos Aires

President: Dr. Martin Ramón Arana, 1809 Rodriguez Peña, Buenos Aires.
General Secretary: Dr. Alfredo Larguia, Cerrito 1179, Buenos Aires.

Associação Paulista de Medicina, Section on Pediatrics

President: Dr. Vicente Lara.
First Secretary: Dr. Armando de Arruda Sampaio.
Second Secretary: Dr. Paulo de Barros Franca, Av. Brigadeiro Luiz Antonio 393, 1° Andar, São Paulo, Brazil.

British Paediatric Association

President: Prof. L. G. Parsons, 58 Calthorpe Rd., Five Ways, Birmingham.
Secretary: Dr. Donald Paterson, 27 Devonshire Pl., London, W. 1.

Danish Pediatric Society

President: Dr. E. Lenstrup, Copenhagen.
Secretary: Dr. E. Gjørup, Dronning Louises Børnehospital, Copenhagen.

Nederlandische Vereeniging voor Kindergeneeskunde

President: Dr. J. H. G. Carstens, Servaasbolwerk 14ª, Utrecht.
Secretary: Dr. R. P. van de Kasteele, Laan van Poot 340,'s Gravenhage.
Place: Different places. Time: Three times a year.

Paediatrický Spolok na Slovensku

President: Dr. A. J. C. Chura, Lazaretská 11, Bratislava.
Secretary: Dr. P. Rados, Lazaretská 6, Bratislava.
Place: Pediatric Clinic, University Bratislava. Time: Six times a year.

Royal Society of Medicine, Section for the Study of Disease in Children

President: Dr. E. A. Cockayne, 98 Harley St., London, W. 1, England.
Secretary: Dr. R. Lightwood, 86 Brook St., London, W. 1, England.
Place: 1 Wimpole St., London. Time: Fourth Friday of each month, 4:15 p. m.

Palestine Jewish Medical Association, Section of Physicians of Children's Diseases

President: Prof. S. Rosenbaum, 26 Bialkstr., Tel Aviv.
Secretary: Dr. A. Brünn, 9 Maazestre, Tel Aviv.

Sociedad Cubana de Pediatria

President: Dr. Angel A. Aballí Arellano, 17 No. 609 Vedado, Habana.
Secretary: Dr. Julio G. Cabrera Calderin, Hospital Mercedes L y 21 (Vedado), Box 2430, Habana.
Place: Cátedra de Clinica Infantil, Hospital Mercedes, Habana. Time: Last Wednesday of every month.

Sociedad Mexicana de Pediatria

President: Dr. Fernando López Clares, 12/a. Medellín 191, Mexico.
Secretary: Dr. Jesus Gómez Pagola, Versalles 64, Mexico.

Sociedad Venezolana de Puericultura y Pediatria

President: Dr. E. Santos Mendoza.
Secretary: Dr. P. Oropeza, Hospital de Niños, Caracas.

Société de Pédiatrie de Paris

President: Dr. B. Weill-Hallé, 49 Avenue Raymond Poincare, Paris, France.
Secretary: Dr. Jean Hallé, 10 bis Rue Pré aux Clercs, Paris, France.
Place: Hôpital des Enfants Malades, 49 Rue de Sèvres. Time: 4:30 p. m.
Place: Hôpital des Enfants Malades, 49 Rue de Sèvres. Time: 4:30 p. m., third Thursday of every month.

Uruguyan Society of Pediatrics

President: Dr. Jose Alberto Praderi, Eduardo Acevedo 1132, Montevideo.
Secretary: Dr. Alfredo Ramon Guerra, Paysandú 824, Montevideo.

NATIONAL

American Medical Association, Scientific Assembly, Section on Pediatrics

Chairman: Dr. Hugh L. Dwyer, 315 Alameda Rd., Kansas City, Mo.
Secretary: Dr. Gilbert J. Levy, 188 S. Bellevue Blvd., Memphis, Tenn.
Place: Chicago. Time: June 12-16, 1944.

American Academy of Pediatrics

President: Dr. Franklin P. Gengenbach, 1850 Gilpin St., Denver, Colo.
Secretary: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.

* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

American Hospital Association, Children's Hospital Section

Chairman: Dr. Joelle C. Hiebert, 299 Main St., Lewiston, Maine.
Secretary: Dr. W. Franklin Wood, McLean Hospital, Waverly, Mass.

American Pediatric Society

President: Dr. James L. Gamble, 300 Longwood Ave., Boston.
Secretary-Treasurer: Dr. Hugh McCulloch, 325 N. Euclid Ave., St. Louis.

Canadian Society for the Study of Diseases of Children

President: Dr. R. R. Struthers, 906 Drummond Medical Bldg., Montreal.
Secretary-Treasurer: Dr. Elizabeth Chant Robertson, Hospital for Sick Children, Toronto.

Society for Pediatric Research

President: Dr. Joseph A. Johnston, Henry Ford Hospital, Detroit.
Secretary: Dr. Mitchell I. Rubin, 1740 Bainbridge St., Philadelphia.

SECTIONAL

Intermountain Pediatric Society

President: Dr. Eugene Smith, 385–24th St., Ogden, Utah.
Secretary-Treasurer: Dr. W. C. Cheney, 837 Boston Bldg., Salt Lake City.
Place: Salt Lake City General Hospital. Time: First Thursday of each month, 8 p. m.

New England Pediatric Society

President: Dr. Warren R. Sisson, 319 Longwood Ave., Boston.
Secretary-Treasurer: Dr. James Marvin Baty, 1101 Beacon St., Brookline, Mass.
Place: Boston Medical Library. Time: Four meetings a year, occurring from September to May.

North Pacific Pediatric Society

President: Dr. M. L. Bridgeman, 1020 S. W. Taylor St., Portland, Ore.
Secretary: Dr. C. G. Ashley, 833 S. W. 11th Ave., Portland, Ore.

Northwestern Pediatric Society

President: Dr. Arild E. Hansen, University of Minnesota, Minneapolis.
Secretary-Treasurer: Dr. Albert V. Stoesser, 205 W. University Hospital, Minneapolis.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

Rocky Mountain Pediatric Society

President: Dr. G. R. Fisher, 23 E. Pikes Peak Ave., Colorado Springs, Colo.
Secretary: Dr. Joseph H. Lyday, 1850 Gilpin St., Denver.

Southern Medical Association, Section of Pediatrics

Chairman: Dr. William Weston Jr., 1428 Lady St., Columbia, S. C.
Secretary. Dr. Angus McBryde, 604 W. Chapel Hill St., Durham, N. C.

STATE

Alabama Pediatric Society

President: Dr. Amas Gipson, 948 Forrest Ave., Gadsen.
Secretary-Treasurer: Dr. Ruth Berrey, 2021–6th Ave. N., Birmingham.

Arizona Pediatric Society

President: Dr. Vivian Tappan, San Clemente, Tucson.
Secretary: Dr. Hilda Kroeger, Arizona State Health Dept. (Maternal and Child Welfare Division), Phoenix.

Arkansas State Pediatric Association

Chairman: Dr. C. B. Billingsley, 1425 N. 11th St., Fort Smith.
Secretary: Dr. R. E. Weddington, 1425 N. 11th St., Fort Smith.

California State Medical Society, Section on Pediatrics

Chairman: Dr. William C. Deamer, University of California Hospital, San Francisco.
Secretary: Dr. Charles W. Leach, 2000 Van Ness Ave., San Francisco.

Florida State Pediatric Society

President: Dr. Ludo Von Meysenbug, Box 3356, Daytona Beach.
Secretary: Dr. Robert Blessing, 409 Blount Bldg., Ft. Lauderdale.
Place: Concurrent with state association meeting at time of convention.

Georgia Pediatric Society

President: Dr. T. F. Davenport, 104 Ponce de Leon Ave. N. E., Atlanta.
Secretary-Treasurer: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.

Hezekiah Beardsley Pediatric Club of Connecticut

President: Dr. Edward T. Wakeman, 129 Whitney Ave., New Haven.
Secretary: Dr. Herman Yannet, Southbury Training School, Southbury.
Time: Three meetings a year.

Illinois State Medical Society, Section on Pediatrics

Chairman: Dr. Craig D. Butler, 715 Lake St., Oak Park.
Secretary: Dr. A. J. Fletcher, 139 N. Vermilion, Danville.

Indiana State Pediatric Society

President: Dr. K. T. Knode, 1105 E. Jefferson Bldg., South Bend.
Secretary-Treasurer: Dr. Mathew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

Iowa Pediatric Society

President: Dr. Mark L. Floyd, Children's Hospital, Iowa City.
Secretary-Treasurer: Dr. James Dunn, Davenport Bank Bldg., Davenport.

MEDICAL SOCIETY OF STATE OF NEW YORK, SECTION ON PEDIATRICS

Chairman: Dr. A. Clement Silverman, 608 E. Genesee St., Syracuse.
Secretary: Dr. Albert G. Davis, 307 Gas and Electric Bldg., Utica.

MEDICAL SOCIETY OF THE STATE OF PENNSYLVANIA, PEDIATRIC SECTION

Chairman: Dr. Elwood W. Stitzel, 403 Central Trust Bldg., Altoona, Pa.
Secretary: Dr. P. F. Lucchesi, Philadelphia Hospital, Philadelphia.

MICHIGAN STATE MEDICAL SOCIETY, PEDIATRIC SECTION

Chairman: Dr. Charles F. McKhann, University Hospital, Ann Arbor.
Secretary: Dr. Mark F. Osterlin, Central Michigan Children's Clinic, Traverse City.

MISSISSIPPI STATE PEDIATRIC SOCIETY

President: Dr. Harvey F. Garrison Jr., 315 E. Capitol Pl., Jackson.
Secretary: Dr. Guy Verner, 126 N. Congress St., Jackson.

NEBRASKA PEDIATRIC SOCIETY

President: Dr. E. W. Hancock, 820 Sharp Bldg., Lincoln.
Secretary-Treasurer: Dr. John M. Thomas, 1102 Medical Arts Bldg., Omaha.
Place: As announced by committee. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

NEW HAMPSHIRE PEDIATRIC SOCIETY

President: Dr. MacLean J. Gill, 14 N. State St., Concord.
Secretary-Treasurer: Dr. Ursula G. Sanders, 46 Pleasant St., Concord.
Time: Twice yearly.

NORTH CAROLINA PEDIATRIC SOCIETY

President: Dr. Thomas M. Watson, Greenville.
Secretary: Dr. Frederick B. Haar, Greenville.

OKLAHOMA STATE PEDIATRIC SOCIETY

President: Dr. Ben H. Nicholson, 301 N. W. 12th St., Oklahoma City.
Secretary: Dr. Luvern Hays, 108 W. 6th St., Tulsa.
Place: Oklahoma Club. Time: 6:30 p. m., fourth Friday of each alternate month from September to May, inclusive.

SOUTH CAROLINA PEDIATRIC SOCIETY

President: Dr. Lonita Boggs, 301 E. Coffee St., Greenville.
Secretary-Treasurer: Dr. Hilla Sheriff, Wade Hampton Office Bldg., Columbia.

TEXAS PEDIATRIC SOCIETY

President: Dr. F. H. Lancaster, 4409 Fannin St., Houston.
Secretary-Treasurer: Dr. John E. Ashby, 3610 Fairmount Ave., Dallas.

VIRGINIA PEDIATRIC SOCIETY

President: Dr. Edwin A. Harper, 301 Rivermont Ave., Lynchburg.
Secretary: Dr. Emily Gardner, 1100 W. Franklin St., Richmond.

WEST VIRGINIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

President: Dr. Andrew Amick, 1021 Quarrier St., Charleston.
Secretary: Dr. A. A. Shawkey, Professional Bldg., Charleston.

LOCAL

ACADEMY OF MEDICINE OF CLEVELAND PEDIATRIC SECTION

Chairman: Dr. J. D. Nourse, 10515 Carnegie Ave., Cleveland.
Secretary: Dr. I. B. Silber, 10465 Carnegie Ave., Cleveland.
Place: Cleveland Medical Library Bldg. Time: October, December, February and April.

ACADEMY OF MEDICINE, TORONTO, SECTION OF PEDIATRICS

President: Dr. I. Nelles Silverthorne, 170 St. George St., Toronto, Canada.
Secretary: Dr. G. P. Hamblin, 2333 Bloor St. W., Toronto, Canada.

BRONX PEDIATRIC SOCIETY

President: Dr. Harry J. Cohen, 1975 Walton Ave., New York.
Secretary: Dr. Walter Levy, 12 E. 88th St., New York.
Place: Concourse Plaza Hotel, 161st St., and Grand Concourse. Time: Second Wednesday of each month, except June, July, August and September.

BROOKLYN ACADEMY OF PEDIATRICS

President: Dr. Harry A. Naumer, 37–8th Ave., Brooklyn.
Secretary: Dr. Lewis A. Koch, 62 Pierrepont St., Brooklyn.
Place: Granada Hotel. Time: Fourth Wednesday of October, November, February, March and April.

BUFFALO PEDIATRIC SOCIETY

President: Dr. A. Wilmot Jacobsen, 187 Bryant St., Buffalo N. Y.
Secretary: Dr. Richard A. Downey, 786 Forest Ave., Buffalo, N. Y.
Place: Children's Hospital, 219 Bryant St. Time: 8:30 p. m., first Monday of each month from September to June.

CENTRAL NEW YORK PEDIATRIC CLUB

President: Dr. Edward J. Wynkoop, 501 James St., Syracuse.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Places:: Various cities in New York. Time: Third Tuesday of April and September.

CHICAGO PEDIATRIC SOCIETY

President: Dr. Heyworth N. Sanford, 952 N. Michigan Ave., Chicago.
Secretary: Dr. Henry G. Poncher, 1819 W. Polk St., Chicago.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May, Inclusive.

Cincinnati Pediatric Society

President: Dr. Lloyd K. Felter, 3144 Jefferson Ave., Cincinnati.
Secretary: Dr. T. Selkirk, 3530 Reading Rd., Cincinnati.
Place: Children's Hospital, Elland Ave., Cincinnati. Time: On call.

Dallas Pediatric Society

President: Dr. John E. Ashby, 3610 Fairmount Ave., Dallas, Texas.
Secretary-Treasurer: Dr. Gladys J. Fashena, 4585 Belfort, Dallas, Texas.
Place: Bradford Baby Hospital. Time: 1 p. m., second and fourth Saturdays of each month.

Detroit Pediatric Society

President: Dr. Hugh Lewis, Detroit, Mich.
Secretary: Dr. John J. Pollack, 622-26 Maccabees Bldg., Detroit, Mich.
Place: Wayne County Medical Society. Time: 8:30 p. m., first Wednesday of each month from October to June, inclusive.

Fulton County Medical Society, Pediatrics Section (Atlanta, Ga.)

Chairman: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.
Secretary: Dr. Harry Lange, 478 Peachtree St., N. E., Atlanta.
Place: Academy of Medicine, 38 Prescott St. N. E. Time: Second Thursday of each month from October to April, 8 p. m.

Houston Pediatric Society

President: Dr. Raymond Cohen, 2300 Caroline St., Houston, Texas.
Secretary: Dr. Betty Moody, 526 Richmond Rd., Houston, Texas.
Place: College Inn, Houston. Time: Fourth Monday of each month.

Kansas City (Missouri) Pediatric Society

President: Dr. Edwin H. Schorer, 1103 Grand Ave., Kansas City.
Secretary: Dr. H. E. Petersen, Kirkpatrick Bldg., St. Joseph, Mo.
Place: Kansas City General Hospital. Time: On call.

Los Angeles County Medical Association, Pediatric Section

President: Dr. Oscar Reiss, 2200 W. 3d St., Los Angeles.
Secretary-Treasurer: Dr. Elena Boder, 1830½ Lucille Ave., Los Angeles.
Place: Los Angeles County Medical Headquarters, 1925 Wilshire Blvd. Time: Second Monday of February, April, June, October and December.

Medical Society of the County of Kings and the Academy of Medicine of Brooklyn, Pediatric Section

President: Dr. Harry Bikoff, 850 St. Marks Ave., Brooklyn.
Secretary: Dr. Henry Rascoff, 895 Eastern Parkway, Brooklyn.
Place: 1313 Bedford Ave., Brooklyn. Time: 9:00 p. m., fourth Monday of each month, October to April, inclusive.

Medical Society of the County of Queens, Inc., Section on Pediatrics

Chairman: Dr. Meyeron Coe, 217-02–91st Ave., Queens Village, N. Y.
Secretary-Treasurer: Dr. Edith A. Mittell, 144–38th Ave., Flushing, N. Y.
Place: Queens County Medical Bldg., Forest Hills, N. Y. Time: Third Monday of October, January, March and May.

Medical Society of the District of Columbia, Section on Pediatrics

President: Dr. Harry A. Spigel, 2647 Connecticut Ave., Washington, D. C.
Secretary-Treasurer: Dr. Perry W. Gard, 2520 Woodley Rd., Washington, D. C.
Place: Medical Society Bldg., 1718 M St. N. W. Time: 8 p. m., fourth Thursday of every month.

Memphis Pediatric Society

President: Dr. F. T. Mitchell, 376 S. Bellevue Ave., Memphis, Tenn.
Secretary-Treasurer: Dr. Harry Jacobson, 1193 Madison Ave., Memphis, Tenn.
Place: John Gaston Hospital. Time: Quarterly.

Milwaukee Pediatric Society

President: Dr. John H. Reynolds, 1628 W. Wisconsin Ave., Milwaukee.
Secretary-Treasurer: Dr. F. J. Mellencamp, 324 E. Wisconsin Ave., Milwaukee.
Place: Milwaukee Athletic Club. Time: Second Wednesday of each alternate month, beginning with February.

New York Academy of Medicine, Section of Pediatrics

Chairman: Dr. Edith M. Lincoln, 600 Park Ave., New York.
Secretary: Dr. Alfred E. Fischer, 73 E. 90th St., New York.
Place: New York Academy of Medicine, 2 E. 103d St. Time: Second Thursday of each month from October to May, inclusive, 8:30 p. m.

Northern California Affiliates

President: Dr. Crawford Bost, 490 Post St., San Francisco.
Secretary: Dr. William A. Reilly, 384 Post St., San Francisco.
Time: Second Thursday of September, November, January, March and May.

Oklahoma City Pediatric Society

President: Dr. William M. Taylor, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. G. R. Felts, 625 N. W. 10th St., Oklahoma City.
Place: Oklahoma Club. Time: Third Thursday of each month.

Philadelphia Pediatric Society

President: Dr. Theodore S. Wilder, Greene and Coulter Sts., Germantown, Philadelphia.
Secretary: Dr. Sherman Little, 1740 Bainbridge St., Philadelphia.
Place: College of Physicians, 19 S. 22d St. Time: Second Tuesday in March, May, October and December.

Pittsburgh Pediatric Society

President: Dr. Carl Ruder, 646 Washington Rd., Mount Lebanon, Pittsburgh.

Secretary-Treasurer: Dr. C. J. Stoecklein, 125 De Soto St., Pittsburgh.

Place: Pittsburgh Academy of Medicine. Time: Second Friday, alternate month from October to June, inclusive.

Richmond Pediatric Society

President: Dr. Stanley Meade, 913 Floyd Ave., Richmond, Va.

Secretary-Treasurer: Dr. Louise Galvin, 214 S. Boulevard, Richmond, Va.

Place: Richmond Academy of Medicine, 1200 E. Clay St. Time: 8 p. m., third Thursday of each month, except June, July and August.

Rochester Pediatric Society

President: Dr. Herbert Soule, 122 Rutgers St., Rochester, N. Y.

Secretary-Treasurer: Dr. Jerome Glaser, 300 S. Goodman St., Rochester, N. Y.

Place: Rochester Academy of Medicine or arrangement by program committee. Time: Third Friday of each month from October to May.

St. Louis Pediatric Society

President: Dr. Jerome Diamond, 508 N. Grand Ave., St. Louis.

Secretary-Treasurer: Dr. Mary A. McLoon, 408 Humboldt Bldg., St. Louis.

Place: St. Louis Medical Society Bldg. Time: First Friday of each month from November to June.

Seattle Pediatric Society

President: Dr. Frederick B. Joy, Stimson Bldg., Seattle.

Secretary: Dr. Sherod M. Billington, Medical Dental Bldg., Seattle.

Place: College Club. Time: Third Friday of each month from September to June at 6:30 p. m.

Southwestern Pediatric Society

President: Dr. Jeanette Harrison, 1136 W. 6th St., Los Angeles.

Secretary: Dr. Henry F. Gallagher, 1930 Wilshire Blvd., Los Angeles.

Place: Jonathan Club of Los Angeles. Time: First Wednesday in January, March, May, September and November.

University of Michigan Pediatric and Infectious Disease Society

President: Dr. Campbell Harvey, 35 W. Huron St., Pontiac, Mich.

Secretary: Dr. Harry A. Towsley, University of Michigan, Department of Pediatrics and Communicable Diseases, Ann Arbor, Mich.

Westchester County Medical Society, Pediatrics Section (New York)

President: Dr. John B. Ahouse, 27 Ludlow St., Yonkers, N. Y.

Secretary-Treasurer: Dr. Elvira Ostlund, 64 Highland Rd., Rye, N. Y.

Place: Grasslands Hospital, Valhalla, N. Y. Time: Third Thursday in October, December, February and April.